New strategy to attenuate pulse wave velocity in haemodialysis patients

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Abstract

Background. Pulse wave velocity (PWV) is commonly elevated in haemodialysis (HD) patients having cardiovascular diseases. Disturbances in calcium–phosphate metabolism are among the established cardiovascular risk factors in HD patients. The present study was performed to assess the effect of sevelamer on PWV in HD patients.

Methods. Fifteen patients, who had been treated with calcium carbonate as a phosphate binder, were entered into the study. Changes in PWV during the 6 months before sevelamer administration were compared with PWV changes during 6 months of receiving sevelamer. Serum biochemistry parameters were also assessed.

Results. Compared with the preceding control period, the sevelamer period resulted in decreased serum calcium (9.9±0.1 to 9.6±0.1 mg/dl, n=15; P<0.01) in association with reductions in oral calcium load (4.3±0.4 to 2.3±0.6 g/day; P<0.001). Serum phosphorus and whole parathyroid hormone remained unchanged. Sevelamer reduced serum total cholesterol (167±7 to 148±6 mg/dl; P<0.001) and LDL-cholesterol (85±8 to 65±7 mg/dl; P<0.001), without modifying HDL-cholesterol or triglycerides. Finally, sevelamer reversed the increase in PWV observed during the control period (from 46±16 to 22±9 cm/s/month; P<0.01).

Conclusions. In chronic HD patients, sevelamer decreased serum total- and LDL-cholesterol as well as calcium. Moreover, our findings suggest that treatment with sevelamer attenuates the progressive increase in PWV observed during calcium carbonate treatment.

Keywords: blood pressure; calcium overload; dyslipidaemia; hyperphosphataemia; parathyroid hormone

Introduction

Haemodialysis (HD) patients frequently develop cardiovascular disease complications and these constitute a major cause of death in this population [1]. Prevention of arteriosclerotic diseases is important among HD patients, not only because it may improve life expectancy but also because it decreases total medical costs for patients with end-stage renal diseases. In addition to traditional cardiovascular risk factors (dyslipidaemia, hyperglycaemia and hypertension), HD patients are commonly exposed to additional risk factors related to uraemia, including hyperparathyroidism, hyperphosphataemia and calcium overload [2–5].

Arteriosclerosis occurs principally in large- and medium-sized elastic and muscular arteries and leads to ischaemia of the heart, brain, kidney, intestine and extremities [2]. Monckeberg medical sclerosis and atherosclerosis are typically seen in muscular and elastic arteries, respectively. Morphological abnormalities in arteriosclerosis, such as atheroma, fibrosis and calcification, contribute to the elevated stiffness of the vessel wall [2,6,7]. Blacher et al. [8,9] recently have developed a non-invasive procedure for quantifying arterial stiffness. The Moens–Korteweg equation provides a theoretical basis which indicates that the square of the pulse wave velocity (PWV) through an artery is directly related to its stiffness. Although PWV does not provide a locus of arteriosclerosis it affords an easy method for repeated measurements of arterial stiffness.

In the present study, we measured PWV as well as lipids [total cholesterol (TC), triglyceride (TG), and low- and high-density lipoprotein cholesterol (LDL-C and HDL-C, respectively)], whole parathyroid hormone (PTH) and blood pressure in HD patients [10,11]. Recent investigations have shown that angiotensin blockade, vitamin E and lipid-lowering drugs, including statins, attenuate increases in PWV in HD patients [12–14]. Sevelamer is a phosphate binder that
does not contain calcium or aluminium. It improves certain cardiovascular risk factors in HD patients and decreases both phosphate and LDL-C [15]. Sevelamer has also been shown to reduce calcium load and to slow the speed of aortic and coronary calcification [16]. However, the effects of sevelamer on PWV have not been assessed yet. PWV is a predictor of cardiovascular survival in HD patients [9,12]. These observations prompted us to examine whether therapeutic manoeuvres, such as addition of sevelamer, would decrease PWV to provide preventative treatment against cardiovascular complications in HD patients.

Subjects and methods

Patients undergoing maintenance HD (4 h/session, 3 days/week) in our clinics were entered into the study after accepting informed consent according to the Declaration of Helsinki [17]. As described previously [14], PWV and ankle–brachial pressure index (ABI) were measured using an automated polygraphy device (AT Form; Nihon Colin Co. Aichi Ltd, Japan) after HD sessions when the patients had reached their own dry weights. PWV was measured using the length from the heart to the posterior tibial artery just above ankle. In recent studies, we validated the usefulness of PWV from the heart to the tibial artery as a marker of arteriosclerosis in HD patients [14]. Indeed, annual changes in aorto-tibial PWV are related to cardiovascular risk factors, such as HD duration, TG and, possibly, to homocysteine levels. PWV is inaccurately low when ABI is markedly decreased, because significant arterial stenosis delays the pulse wave. We therefore analysed PWV data from the patients who showed ABI above 1.0 throughout observation periods.

We then carried out a prospective study. We excluded patients with marked hyperparathyroidism (whole PTH > 200 pg/ml), because hyperparathyroidism appears to accelerate the progression of arteriosclerosis [4,7]. Whole PTH was evaluated because it estimates agonistic activity of PTH [11]. Thus, patients who received vitamin D pulse therapy were excluded automatically. PWV was assessed in 20 patients in March 2003 and again in September 2003, followed by onset of sevelamer treatment (RenaGel; Chugai Pharmaceuticals, Tokyo, Japan). Calcium carbonate intake was decreased with sevelamer to maintain phosphate levels at a target of 5.5 mg/dl. Blood pressure and biochemical parameters were measured at least monthly throughout the observation periods and averages were calculated for each period (before and during sevelamer treatment). We have demonstrated recently that antihypertensive medication, lipid-lowering drugs and dialysis membrane type affect PWV [14]. We therefore used data from patients who maintained an unchanged medication and dialysis membrane for 1 year for the final analysis. Five patients dropped out of the study: one died from prostate cancer during the control period, another discontinued sevelamer because of invertebrate constipation, a third was required to change the dialysate [vitamin E-coated (CLEE-15N; Asahi Medical Co. Ltd, Tokyo, Japan) to polysulphone (APS-15S; Asahi Medical Co. Ltd)] due to marked itching and the final two patients moved. In March 2004, PWV was measured in 15 patients. Many HD patients show no change in PWV following a reduction in blood pressure [12]. Nevertheless, blood pressures did not change throughout the entire observation period in the present study (Table 1). Therefore, PWVs were unadjusted for blood pressure, unless otherwise stated.

The data from 15 patients (four females) were used for final analysis. Patient age and HD duration averaged 54±3 and 10±2 years, respectively. Diabetic patients were excluded. Twelve patients were receiving angiotensin blockade treatment [angiotensin-converting enzyme inhibitors (capotril 25–50 mg/day, temocapril 4 mg/day, trandolapril 1 mg/day, imidapril 5 mg/day) or angiotensin receptor blockers (losartan 100 mg/day, valsartan 80 mg/day, candesartan 8 mg/day)] and four patients were taking lipid-lowering drugs (pravastatin 10 mg/day, atrovastatin 10 mg/day, niconerital 375 mg/day). All medications had been prescribed ≥6 months before the study and doses were maintained constant throughout the entire observation period (except calcium carbonate and sevelamer).

Data are expressed as means±SEM. Analysis of variance and Student t-tests with or without Bonferroni correction were used [10]. There were significant temporal differences for PWV as well as for doses of calcium carbonate and sevelamer, serum calcium, TC and LDL-C (see below). Thus, changes in these parameters were entered into multiple regression analysis against alterations in PWV. Since multiple regression revealed a contribution for decreases in calcium carbonate intake to reductions in PWV, we performed a linear regression analysis between these two parameters. A P-value of <0.05 was considered statistically significant.

Results

Figure 1 shows changes in calcium carbonate doses, in serum calcium and phosphate and in whole PTH concentrations. Calcium carbonate intake was decreased markedly by replacement with sevelamer (4.3±0.4 to 2.3±0.6 g/day, n = 15; P < 0.001). While there were substantial variations among patients, 750 mg sevelamer corresponded to ~500 mg calcium carbonate in ability to control phosphate. Thus, the average dose of sevelamer was 2.9±0.2 g/day. In association with the reduced calcium load, serum calcium significantly declined (9.9±0.1 to 9.6±0.1 mg/dl; P < 0.01). However, serum phosphate (5.8±0.1 to 5.9±0.2 mg/dl) and whole PTH (46±5 to 47±7 pg/ml) were not altered. Although the calcium–phosphate product tended to decrease during sevelamer administration (57.5±1.2 to 56.3±1.4 mg²/dl²; P = 0.08), this change did not attain statistical significance. Figure 2 summarizes sevelamer-induced changes in serum lipids. Sevelamer substantially decreased both TC (167±7 to 148±6 mg/ml; P < 0.001) and LDL-C (85±8 to 65±7 mg/dl; P < 0.001). However, sevelamer did not influence HDL-C (58±5 to 58±4 mg/dl) or TG levels (96±9 to 98±9 mg/dl).

Figure 3 depicts increases in PWV before and during sevelamer administration. In March 2003, basal PWV averaged 1182±54 cm/s with a corresponding blood pressure of 143±4/81±2 mmHg and PWV/SBP (systolic blood pressure) was 8.3±0.4 cm/s/mmHg. In September 2003, PWV increased to 1456±120 cm/s (P < 0.05) at a blood pressure of 142±4/80±2 mmHg.
Table 1. Temporal profiles of clinical parameters

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SBP, systolic blood pressure; DBP, diastolic blood pressure; s-Ca, serum calcium.
and PWV/SBP was also augmented to 10.2 ± 0.8 cm/s/mmHg (P < 0.05). Before sevelamer, PWV increased progressively at the rate of 45 ± 16 cm/s/month (P < 0.01 vs 0). Surprisingly, the acceleration in PWV was arrested during sevelamer therapy (−20 ± 9 cm/s/month). In March 2004, mean PWV was 1334 ± 90 cm/s with a blood pressure of 144 ± 4/82 ± 2 mmHg and PWV/SBP averaged 9.3 ± 0.6 cm/s/mmHg. Our previous results using calcium carbonate as a phosphate binder indicated that longer durations of HD are associated with faster PWV [14]. In the present study, PWV would have increased elevation more rapidly during the post-control period than the control period unless sevelamer had been administered. In addition, sevelamer did not alter systolic (143 ± 3 to 142 ± 4 mmHg) or diastolic blood pressure (81 ± 1 to 80 ± 2 mmHg). Similarly, dry weight remained unchanged between the control (60.9 ± 3.2 kg) and sevelamer periods (60.9 ± 3.2 kg). Multiple regression demonstrated that alterations in calcium carbonate intake were significantly related to changes in PWV (P < 0.05), whereas doses of calcium carbonate and sevelamer, serum calcium, TC and LDL-C were not. Figure 4 illustrates the relationship between changes in both PWV and calcium carbonate intake. The magnitude of decrease in PWV was correlated significantly with changes in calcium carbonate intake (r = 0.60, P < 0.05). The changes in other parameters, such as in serum calcium, lipids (TC or LDL-C) and doses of sevelamer, did not show significant linear correlations with PWV.

Discussion

The pathogenesis of arteriosclerosis involves multiple processes that include the physical factors of high blood pressure, metabolic factors, such as dyslipidaemia, hyperhomocysteinaemia and PTH, and inflammatory factors, such as reactive oxygen species and C-reactive protein [2,4,6]. Furthermore, derangements in protective factors, such as in HDL-C, also participate in the development of arteriosclerosis [2]. Recent investigations have revealed important roles for growth factors and cytokines in arteriosclerosis [6].

Our present results indicate that sevelamer decreased TC and LDL-C. These data are consistent with those of Burke et al. [15] who showed that sevelamer decreased LDL-C in HD patients. In addition, we found recently that oxidized LDL increased in parallel with LDL-C in HD patients [10]. Thus, it is likely that oxidized LDL, which triggers atherosclerosis [2], was reduced by sevelamer. Although sevelamer did not alter HDL-C or TG in the present study, larger doses of the drug may have influenced these lipids [15]. Nevertheless, greater doses of sevelamer have been shown to reduce patient compliance due to alterations in bowel habit (constipation). The present study revealed that sevelamer did not affect blood pressure, suggesting that the reductions in PWV were not attributable to changes in blood pressure [8,9,12]. Taken together, these results suggest that sevelamer helps maintain vascular health in HD patients.

Sevelamer caused a significant decrease in serum calcium. However, the degree of reduction in serum calcium was insufficient to induce an increase in PTH [18,19]. This is partly because the change from calcium carbonate to sevelamer in our patients did not cause further reductions in serum phosphate [3,15,18]. Barenbrock et al. [4] showed that hyperparathyroidism affected arterial distensibility even in normotensive
patients. Thus, we excluded patients with marked hyperparathyroidism from this study. Further investigations will be required to assess the effects of sevelamer on arteriosclerosis in HD patients with marked hyperparathyroidism. It is possible that the lack of PTH increase during sevelamer treatment was due to the administration of alfacalcidol (0.25–0.5 μg/day) that we gave to all 15 patients [20]. Collectively, the present observations suggest that sevelamer-induced decreases in serum calcium are modest and should not worsen hyperparathyroidism.

As shown in Figure 4, the decrements in calcium carbonate intake were positively correlated with the degree of PWV attenuation. Indeed, multiple regression analysis revealed that the decreases in calcium carbonate intake contributed strongly to the slowing of PWV increases in HD patients ($R = 0.70, P < 0.05$). Calcium overload appears to promote arterial calcification in HD patients. Blacher et al. [21] demonstrated that the presence and extent of vascular calcification were strong predictors of cardiovascular and all-cause mortality in HD patients. In addition, Haydar et al. [22] showed that PWV was correlated with the degree of coronary calcification in HD patients. Calcium overload has been identified as one of the cardiovascular risk factors in HD patients [5]. While the present data cannot exclude other possible mechanisms, our findings are compatible with those of Chertow et al. [16], who showed that sevelamer slows aortic and coronary calcification and suggested that sevelamer at the doses used in this study arrests the increments in PWV, at least in part, by decreasing calcium load in HD patients.

PWV is considered to be a surrogate risk factor for cardiovascular diseases. In HD patients, higher PWV indicates a shorter survival [9,12]. In the present study, sevelamer slightly decreased serum calcium during the last PWV measurement. Elevations in extracellular calcium cause increases in cardiovascular reactivity [23], suggesting that sevelamer-induced decreases in calcium concentration may have reduced cardiac contractility. Thus, reductions in PWV by sevelamer may reflect not only morphological improvements in the arterial wall but also improvement in cardiovascular function. These possibilities make it more careful to interpret PWV data. Although long-term large-scale studies will be required for more definitive analysis, our results suggest that sevelamer could elicit favourable outcomes in HD patients, presumably by retarding the progression of arteriosclerosis.

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Conflict of interest statement. None declared.

References


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