Increase of Low Serum Concentrations of High-Density Lipoprotein (HDL) Cholesterol in TIA-Patients Treated with Phenytoin

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SUMMARY Serum high density lipoprotein (HDL) cholesterol and other lipoproteins were measured in 27 TIA-patients with a mean age of 49 ± 10 years before and during phenytoin therapy. The pretreatment concentrations of HDL-cholesterol (mmol/l, mean ± sd) were lower (p < 0.001) in male (1.03 ± 0.25) and in female patients (1.15 ± 0.44) than in healthy male (1.28 ± 0.34) and female controls (1.52 ± 0.31) respectively. After one month’s phenytoin therapy HDL cholesterol concentrations reached normal levels (men 1.33 ± 0.38, women 1.61 ± 0.27) and after 9 months of therapy even surpassed them (men 1.47 ± 0.27, p < 0.05; women 1.91 ± 0.33, p < 0.01). Percent increase of HDL cholesterol after 9 months of therapy was 42 ± 25 in men and 68 ± 46 in women. There was a positive correlation (r = 0.43, p < 0.05) between serum phenytoin level and increase of HDL cholesterol. HDL/LDL cholesterol ratio increased (p < 0.01) also during 9 months of therapy (men from 0.26 ± 0.05 to 0.36 ± 0.10, women from 0.26 ± 0.07 to 0.43 ± 0.13) and showed a positive correlation (r = 0.91, p < 0.001) with increase of serum HDL cholesterol. The HDL cholesterol levels achieved have been maintained with a mean serum phenytoin level of 5.6 ± 3.6 mg/l. Phenytoin induced increase in serum HDL levels should not yet be equated with protection against atherosclerosis.

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A LOW SERUM CONCENTRATION of high density lipoprotein (HDL) is associated with an increased risk of ischemic heart disease and low serum HDL cholesterol concentrations have also been reported in patients with TIA and in patients with ischemic brain infarction. These observations have raised the hypothesis that increased serum HDL concentration could retard the development of ischemic heart disease and ischemic cerebrovascular disease. There are only a few factors which are known to increase serum HDL. The site and mechanism of serum HDL synthesis in human liver are not known, but the smooth endoplasmic reticulum, which is the main subcellular structure stimulated by drugs, is thought to be the site in liver cells where lipoprotein lipids are synthesized and organized into particles. Because phenytoin is one of the most potent pharmacological liver microsomal inducers we decided to study the effects of phenytoin on serum HDL cholesterol concentration in TIA-patients.

Patients and Methods

Twenty-seven TIA-patients with a mean age of 49 ± 10 years volunteered for the study after full explanation of the purpose, nature and risks of the study. The study protocol was approved by the Ethical Committee of the University Central Hospital, Helsinki and the Medical Faculty, University of Helsinki, Finland. Informed consent was obtained from the volunteers. The patients had been diagnosed and treated at the Department of Neurology, University of Helsinki, for TIA-related to the carotid or vertebral-basilar systems.
The residual area, obtained by dividing the last concentration-time curve. The area until the last observed is the total area under the serum concentration by the elimination rate constant, was added. \( V_d \) represents the apparent volume of antipyrine distribution, \( D \) is the dose of antipyrine. The daily dosage of phenytoin (diphenylhydantoin) was 200–300 mg divided into two equal doses.

The results are expressed as mean ± 1 sd. To reduce errors caused by possible temporary changes the following calculations were made: in each patient the mean of the two pretreatment serum levels of lipids, lipoproteins and gamma glutamyl transpeptidase activity were regarded as basal pretreatment values.

Student’s t-test was used in statistical comparisons. A simple linear regression was calculated between serum phenytoin level and percent increase of serum HDL cholesterol concentration, between percent increase of serum HDL cholesterol concentration and percent increase of serum HDL/LDL cholesterol ratio, and also between percent increase of the total clearance of antipyrine and percent increase of serum HDL cholesterol concentration.

### Table 2  Serum Lipids and Lipoproteins (mmol/l, mean ± SD) in Healthy Female Controls (n = 49) and in Female TIA-Patients (n = 11) Treated with Phenytoin

<table>
<thead>
<tr>
<th></th>
<th>Before phenytoin</th>
<th>Patients on phenytoin (months)</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>6.19 ± 1.04</td>
<td>6.59 ± 0.99</td>
<td>6.90 ± 1.25</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>1.15 ± 0.44</td>
<td>1.61 ± 0.27</td>
<td>1.69 ± 0.37</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>4.63 ± 1.00</td>
<td>4.47 ± 0.90</td>
<td>4.55 ± 1.32</td>
</tr>
<tr>
<td>VLDL-cholesterol</td>
<td>0.41 ± 0.23</td>
<td>0.50 ± 0.18</td>
<td>0.32 ± 0.13</td>
</tr>
<tr>
<td>Total triglyceride</td>
<td>1.30 ± 0.46</td>
<td>1.62 ± 0.62</td>
<td>1.30 ± 0.37</td>
</tr>
<tr>
<td>HDL-triglyceride</td>
<td>0.22 ± 0.06</td>
<td>0.27 ± 0.06</td>
<td>0.25 ± 0.07</td>
</tr>
<tr>
<td>LDL-triglyceride</td>
<td>0.42 ± 0.09</td>
<td>0.42 ± 0.09</td>
<td>0.41 ± 0.07</td>
</tr>
<tr>
<td>VLDL-triglyceride</td>
<td>0.66 ± 0.42</td>
<td>0.93 ± 0.64</td>
<td>0.64 ± 0.41</td>
</tr>
<tr>
<td>HDL/LDL cholesterol ratio</td>
<td>0.26 ± 0.07</td>
<td>0.37 ± 0.10</td>
<td>0.39 ± 0.09</td>
</tr>
</tbody>
</table>

HDL = High-density lipoprotein, LDL = Low-density lipoprotein, VLDL = Very-low-density lipoprotein

*\( p < 0.05 \), \( \bar{p} < 0.01 \), \( \bar{p} < 0.001 \) for the difference patients/controls

\( \bar{p} < 0.05 \), \( \bar{p} < 0.01 \), \( \bar{p} < 0.001 \) for the difference off/on phenytoin

Conversion: SI to traditional units — Cholesterol: 1 mmol/l ≈ 38.7 mg/100 ml. — Triglyceride: 1 mmol/l ≈ 88.5 mg/100 ml.
Results

The cholesterol and triglyceride concentrations in whole serum and in lipoproteins of controls and phenytoin treated TIA-patients before and after therapy began are given in tables 1 and 2.

Phenytoin induced a raise in HDL cholesterol during the first month in all female patients (fig. 1) and in most male patients (fig. 2). Furthermore, two male patients who did not increase their HDL cholesterol during the first month did so after 3 months of therapy.

In the beginning of the study our TIA-patients had significantly lower serum HDL-cholesterol concentrations than did the healthy controls. During the first months of therapy, serum HDL cholesterol concentrations achieved the levels in healthy controls and after 9 months of therapy significantly surpassed the levels of health controls (tables 1 and 2). There were considerable inter-individual differences in the effect of phenytoin on serum HDL cholesterol concentration. After 3 months of therapy, there was, however, a positive correlation between serum phenytoin level and percent increase of serum HDL cholesterol concentration (fig. 3). Percent increase of HDL cholesterol after 9 months of phenytoin therapy was 42 ± 25 in men and 68 ± 46 in women.

Not only did serum HDL cholesterol concentration
increase, but so did HDL/LDL cholesterol ratio (tables 1 and 2). In addition, there was a positive correlation between percent increase of serum HDL cholesterol and percent increase of serum HDL/LDL cholesterol ratio (fig. 4).

The HDL cholesterol levels achieved have been maintained with a mean serum phenytoin concentration of 5.6 ± 3.6 mg/l (fig. 5). No serious complication of long-term phenytoin therapy has been encountered during the study. One patient suffered a temporary rash which subsided during a break of phenytoin.

The effectiveness of phenytoin in inducing liver microsomes was revealed by more than two-fold shortening of antipyrine elimination half-life (table 3). The same liver microsomal enzyme induction was also revealed by a significant increase of serum gamma glutamyl transpeptidase activity (table 3). There was a positive correlation between percent increase of the total clearance of antipyrine and percent increase of serum HDL cholesterol ($r = 0.78, p < 0.001$).

Seven patients had recurrent TIAs but none suffered brain infarction or myocardial infarction during the study.

**Discussion**

Our results demonstrate that a low serum HDL-cholesterol level often present in TIA-patients can be increased with phenytoin therapy. Increase of low serum HDL could retard the development of serious atherosclerotic complications such as myocardial infarction or stroke, if a low serum HDL is associated with impaired clearance of cholesterol from the arterial wall as has been suggested.15

Patients volunteered for the study before their serum HDL cholesterol levels were measured. We did not select the patients according to their HDL cholesterol levels and the levels detected probably represent an average of HDL cholesterol concentration in TIA-patients in a south Finnish urban area. A low serum HDL is known to precede clinical coronary heart disease.1 This correlates with our experience, that TIA is not only a warning sign of stroke but also a warning sign of myocardial infarction16 and the same seems also to hold true for Americans.17 18

Although there is no clear evidence to show that a drug-induced increase in HDL would modify the course of atherosclerosis,19 there is some indirect evidence to suggest this possibility. We have detected high HDL cholesterol concentrations in epileptic patients treated with phenytoin20 and two independent reports have recently mentioned that many clinicians taking care of epileptic patients have been impressed by the low incidence of myocardial infarction among them.21 22

Intervention that increases HDL levels cannot yet be equated with protection against atherosclerosis23 and the present trial only demonstrates that a low serum HDL cholesterol can be increased with phenytoin therapy. Interventions like ours could, however, be one alternative to correct lipid abnormalities. Phenytoin induced increase of HDL could retard the development of coronary heart disease or stroke as well or perhaps even better than hypolipidemic treatments.

An effort to prevent the progression of atherosclerosis does not, of course, reduce the role of other preventive treatments such as anticoagulants, antiplatelet therapy or vascular surgery in the treatment of TIA-patients. However, the hypothesis that increased serum HDL could retard the development of atherosclerosis offers a specific advantage, i.e., it might also retard the development of coronary heart disease. Be-
cause patients with ischemic cerebrovascular disease often succumb in coronary heart disease,\(^6\) this viewpoint deserves appropriate attention.

There are only a few factors which are known to increase serum HDL. Most of these: estrogenic hormones, chlorinated hydrocarbon insectides, extensive endurance exercise and ethanol are not suitable for clinical therapy of low serum HDL. Phenytoin is one of the most potent liver microsomal inducers and is also suitable for preventive therapy. We do not know if phenytoin increased serum HDL cholesterol levels in our patients by inducing liver microsomes, but this seems to be a probable explanation.\(^26\) Furthermore, the shortened elimination half-life of antipyrine, a positive correlation between percent increase of the total clearance of antipyrine and percent increase of serum HDL cholesterol and the increased activity of serum gamma glutamyl transpeptidase all support this assumption.

Although we prescribed daily doses of 200–300 mg of phenytoin, the serum levels in our patients were suboptimal compared with the therapeutic levels achieved with these doses in the treatment of epilepsy. Since we could not give any assurance that the treatment studied would change the outcome of patients with TIA, our volunteers might have been less motivated to take the medication regularly. Even with these modest serum phenytoin levels, one month’s therapy was enough to increase serum HDL cholesterol to normal levels and after 9 months of therapy HDL cholesterol concentrations in our TIA-patients significantly surpassed the levels in healthy controls. We have detected the highest concentrations of serum HDL cholesterol and apoprotein A-I in those epileptic patients whose serum phenytoin was within therapeutic range.\(^20\) Accordingly it seems possible that if our patients had more carefully followed the dosage prescribed it would have resulted in even higher increases of serum HDL cholesterol.

Not only did serum HDL cholesterol increase but so also did HDL/LDL cholesterol ratio. This ratio has been suggested to provide an improved estimate of the risk of coronary heart disease.\(^1\) This could also hold true in the case of ischemic cerebrovascular disease. Furthermore, measurement of HDL cholesterol or HDL/LDL cholesterol ratio seems to offer a better estimate of abnormalities in lipid metabolism than does the measurement of total lipids.\(^6\) Disturbances of lipid metabolism in our patients would have been overlooked if total cholesterol concentrations only had been measured.

In conclusion, many TIA-patients have a low serum HDL cholesterol concentration which is known to be an independent risk factor for coronary heart disease and which may also be a risk factor for stroke. Once detected a low serum HDL cholesterol can be increased with phenytoin therapy which could retard the development of serious atherosclerotic disorders such as myocardial infarction or brain infarction. The hypothesis that phenytoin-induced increase in HDL levels could retard the development of atherosclerotic complications is yet unproven.

### Acknowledgments

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### References


### Table 3: Effect of Phenytoin Therapy on Serum Gamma-Glutamyl Transpeptidase Activity (γ-GT, U/L, mean ± SD) and Antipyrine Half-Life (T\(_{\text{1/2}}\), HR, Mean ± SD) in TIA-Patients

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>γ-GT</th>
<th>T(_{\text{1/2}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>46.8±62.0</td>
<td>118.2±87.1*</td>
</tr>
<tr>
<td>1</td>
<td>118.2±87.1*</td>
<td>131.4±81.4*</td>
</tr>
<tr>
<td>9</td>
<td>131.4±81.4*</td>
<td>111.4±96.4*</td>
</tr>
<tr>
<td>15</td>
<td>111.4±96.4*</td>
<td>121.3±85.6*</td>
</tr>
<tr>
<td>21</td>
<td>121.3±85.6*</td>
<td>80.4±65.6</td>
</tr>
<tr>
<td>women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>15.8±11.5</td>
<td>88.9±105.6*</td>
</tr>
<tr>
<td>1</td>
<td>88.9±105.6*</td>
<td>90.8±90.3*</td>
</tr>
<tr>
<td>9</td>
<td>90.8±90.3*</td>
<td>77.4±61.9*</td>
</tr>
<tr>
<td>15</td>
<td>77.4±61.9*</td>
<td>68.8±46.1</td>
</tr>
<tr>
<td>21</td>
<td>68.8±46.1</td>
<td>80.5±61.5*</td>
</tr>
</tbody>
</table>

* \(p < 0.05\)
† \(p < 0.01\)
‡ \(p < 0.001\)
Cerebral Embolism in the Michael Reese Stroke Registry

L.R. Caplan, D.B. Hier, and I. D'Cruz

SUMMARY Infarction secondary to cerebral embolism was diagnosed in 127 (23.5%) of 540 patients in the Michael Reese Stroke Registry. Coronary artery disease, atrial fibrillation, valvular heart disease, mitral annulus calcification, and cardiomyopathy were the commonest etiologies. Echocardiography documented a potential embolic source in 7 patients without previously known heart disease, and clarified the cardiac pathology in many of the patients with known heart disease. The left anterior circulation was affected in 48%, right anterior in 37%, and posterior circulation in 15% of patients. CT was abnormal in 71% of the patients, and was approximately equally helpful in all locations. Nineteen percent of emboli presented with a deficit that was other than maximal at onset. Concurrent systemic embolism was unusual (2.3%). Prognosis was somewhat worse than in thrombotic stroke. Grouping of patients according to embolic source (intra-arterial, cardiac, and uncertain source) showed no differences in activity at onset, early course, or in subsequent course of the illness.

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CLINICAL CONCEPTS OF CEREBRAL EMBOLISM have changed dramatically during the past decade. Before 1970, embolism was seldom diagnosed; criteria for diagnosis usually included at least two of the triad of (1) known cardiac source (recent myocardial infarct or rheumatic mitral stenosis with atrial fibrillation), (2) sudden, maximal at onset neurological deficit, and (3) associated systemic embolism. When cerebral angiography became commonplace, atherosclerotic plaques in the extracranial arteries were identified as a source for intra-arterial emboli. Matsumoto et al. recognized that the 8% of 993 strokes attributed to embolism at the Mayo Clinic between 1955 and 1969 underestimated embolism because diagnosis depended upon awareness of a known source.1 Strokes are readily separated into a hemorrhagic group (subarachnoid and intracerebral hemorrhage) and ischemic group but further division of the ischemic group into thrombotic and embolic mechanisms is often difficult and controversial. Dalsgaard-Nielsen considered thrombosis and embolism together3 and the National Cooperative Study Group even coined the term "thorem" to indicate those instances when the differentiation between thrombosis and embolism could not be made with certainty.4 The Harvard Cooperative Stroke Registry estimated that fully 31% of their 694 patients had cerebral embolism,3 a figure far higher than any prior study.1,6-8 The Harvard registry noted (1) atrial fibrillation was an important cause of embolism even without fresh cardiac infarction or valvular disease, (2) embolism did not always cause a deficit that was maximal at onset, (3) systemic embolism was rarely recognized in patients with cerebral emboli, (4) cerebral angiography often documented distal embolism if performed within 48

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