Table. Clinical Characteristics and Drug Levels in Patients with Suppression of Recurrent Syncope

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Trigger</th>
<th>Pathologic Abnormality</th>
<th>Failed Therapy</th>
<th>Levels of Diphenylhydantoin/Carbamazepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>Male</td>
<td>Gossopharyngeal neuralgia</td>
<td>Squamous-cell carcinoma of larynx</td>
<td>Fluooracitine</td>
<td>11.2/4.3</td>
</tr>
<tr>
<td>2</td>
<td>54</td>
<td>Male</td>
<td>Gossopharyngeal neuralgia</td>
<td>Surgery for squamous-cell carcinoma of neck</td>
<td>UCD pacemaker</td>
<td>19/4.8</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>Male</td>
<td>Retinal mediostion</td>
<td>After stellate removal for the Eagle syndrome</td>
<td>Fludrocoroton, stranol, and disopyramide</td>
<td>5.5/3.5</td>
</tr>
<tr>
<td>4</td>
<td>41</td>
<td>Male</td>
<td>Carotic sinus hypersensitivy</td>
<td>Lymphohostesia of neck</td>
<td>Epinephrine</td>
<td>12.8/2.3</td>
</tr>
</tbody>
</table>

* CDD = both atra and variates are boxed and revised.
1 Therapeutic levels: diphenylhydantoin, 18 to 20 μg/mL; carbamazepine, 8 to 12 μg/mL.

An extreme example of the danger of Dr. Jain's exclusive use of relative risk is the way in which information about risk for thromboembolism with oral contraceptive pills was presented in the United Kingdom (2, 3). The official statement, that "combined oral contraceptives containing desogestrel and gestodene are associated with around a two-fold increase in the risk of thromboembolism, caused enormous concern for women and their physicians. Women stopped taking oral contraceptives, resulting in unwanted pregnancies and increased abortions (3)."

For one woman to have a thromboembolic event while receiving the combined oral contraceptive compared with older preparations, the relative risk is 2.0 (95% CI, 1.1 to 3.7) and the NNT is 6700 (CI, 3600 to 54 000). Telling a woman that she has a risk for thromboembolism that has doubled because of the type of pill she takes compares poorly with telling her that yes, there is an increased chance, that we think the size of that chance is 1 in about 7000, but that the uncertainty ranges from 1 in 3600 to 1 in 54 000. For comparison, in the United Kingdom, the chance of being killed in an automobile accident in any one year is 1 in 16 000. Any decision the woman makes may well change depending on the way the information is framed, just as it did for physicians (1). We think that NNTs are useful, and in our Annals paper we discussed ways in which changes in baseline risks for individual patients might be handled. The power of systematic reviews combined with NNTs is that they allow us to see more clearly the choices between several treatments applicable to patients with similar or identical conditions. An example is the use of NNTs for the relative efficacy of oral analgesics for postoperative pain relief (4).

Management of Refractory Neurocardiogenic Syncope

To the Editor: Therapy for neurally mediated syncope and related syndromes has recently received considerable attention. Few randomized trials of any specific therapeutic agents have been performed. β-blockers, nondihydropyridines, theophylline, serotonin receptor blockers, disopyramide, and peripheral vasodilators (α-agonists) have all been used with some success (1). There still remains, however, a group of patients whose condition is refractory to medical and pacing therapy. We describe four patients with refractory, disabling neurocardiogenic syncope whose symptoms improved markedly after therapy with diphenylhydantoin and carbamazepine after drug or pacemaker therapy had failed.

The clinical characteristics and drug levels associated with suppression of recurrent syncope are summarized in the Table. Three patients had a tunnel of the neck region, and one had previously undergone neck surgery. We hypothesize that the gossopharyngeal nerve or carotid body may act as a trigger for activation of vagal afferents to the brainstem, leading to a mixed vasodepressor and vaso- inhibitory response similar to that seen in patients with neurally mediated syncope and its variants. We speculate that these agents may be effective because of the inhibitory effect of diphenylhydantoin and diphenylhydantoin on brainstem activity, although the actual level of the reflex arc is affected by these drugs is not known (2, 3). The exact mechanism by which these agents suppress the automatic reflex involving syncope is unknown.

Kenneth A. Ellenbogen, MD
Mark A. Wood, MD
Hermes A. Kounts, MD, PhD
Medical College of Virginia
Richmond, VA 23298

References

Hypertriglyceridemia and Atherosclerosis

To the Editor: I may be able to shed some light on the quandary concerning the role of triglycerides in the pathogenesis of atherosclerotic disease, as voiced by Dr. Ginsberg in his recent editorial (1). I am the chief investigator for the Bowling Green Study of the primary and secondary prevention of atherosclerotic disease (2, 3). To date, I have compiled an age and sex registry of 668 patients who developed some form of the disease between 4 November 1974 and 1 January 1997.

The Bowling Green Study uses as its lipid predictor the cholesterol retention fraction (low-density lipoprotein (LDL) - high-density lipoprotein (HDL))/LDL. Abnormal fractions are 0.30 or higher, another indicator of abnormality is an LDL cholesterol level of 170 mg/dL (4.4 mmol/L) or greater. According to the Framingham Heart Study guidelines and with a triglyceride level
of 150 mg/dL (1.7 mmol/L) or greater, pure hypertriglyceridemia would occur if the cholesterol reduction fraction is 0.69 or less, the LDL cholesterol level is 169 mg/dL or less, and the triglyceride level is 50 mg/dL or greater. (In the early days of the Bowling Green Study [from 1974 to 1978], data on LDL and HDL cholesterol were not available; thus, a cholesterol disorder was considered to be present if the total cholesterol level was 250 mg/dL [6.5 mmol/L] or more. The 250 mg/dL level was chosen because at this level the LDL cholesterol level is almost always elevated; below this level, no abnormality could be inferred with certainty.)

Green above the 267 male patients with atherothrombotic disease and 229 female patients with the disease had sufficient lipid data with which to determine cholesterol and triglyceride disorders. Pure hypertriglyceridemia was seen in only 9% of the men and 17% of the women. Of the men with pure hypertriglyceridemia, only 20% had never smoked cigarettes; the respective figure for women was 47%. The mean age at disease onset was 71 years; for these men, 76 years for these women.

Twenty-two percent of male patients and 25% of female patients were normolipidemic according to the criteria I described. Of the normolipidemic men, only 19% had never smoked cigarettes; the respective percentage for women was 65%. The mean age at disease onset was 79 years for these men and 77 years for these women.

The point I wish to make is that pure hypertriglyceridemia is uncommon in patients with atherothrombotic disease. When the disease occurs in this scenario, it does so late in life. There may be some disadvantage to the pure hypertriglyceridemic state in men with the disease, but not in women. Unfortunately, even this conclusion is subject to question because most patients in our registry with atherothrombotic disease and pure triglyceridemia who never smoked cigarettes were also hypertensive, with variable degrees of glucose tolerance. I therefore conclude that pure hypertriglyceridemia does not warrant treatment.

W.E. Feeman Jr., MD
Bowling Green, OH 43402

References

To the Editor: Dr. Ginsberg's recommendations for treatment of hypertriglyceridemia (1) are not supported by currently available evidence. First, Dr. Ginsberg offers potential biochemical rationales for why hypertriglyceridemia could cause atherosclerosis. Unfortunately, these explanations are not convincing but are an insufficient basis for establishing clinical policy. Second, he correctly notes that the observational data are inconsistent; indeed, most data do not support an independent role for hypertriglyceridemia in this process (2). Third, he cites the Helsinki Heart Study as the primary clinical trial evidence for lowering triglyceride levels to reduce risk for coronary heart disease. However, analyses from this study showed that the risk reduction provided by gemfibrozil treatment was attributed to changes in levels of cholesterol substrates, not only triglyceride levels; this was also true of patients with type IV hyperlipidemia (3). Similar analyses were done in the Coronary Drug Project; the Lipid Research Clinics Coronary Primary Prevention Trial; and the National Heart, Lung, and Blood Type II studies; in each of these trials, no significant associations were seen between changes in triglyceride levels and changes in risk for coronary heart disease (2). Dr. Ginsberg also mentions the triglyceride–cholesterol interaction found in the Helsinki study; this post hoc finding is not consistent with some other analyses of triglyceride–cholesterol interactions and requires greater confirmation before it can be advocated for general clinical use (4).

Finally, Dr. Ginsberg recommends niacin, statins, or gemfibrozil for treatment of hypertriglyceridemia if diet fails. Given the serious paucity of data supporting a benefit of lowering triglyceride levels, it seems particularly ill-advised to prescribe drugs that are associated with serious side effects, great expense, or elevated risk for conditions other than coronary heart disease (5). Until better evidence becomes available, physicians would be better advised to put their energies into recommending the many well-proven preventive measures for reducing risk for coronary heart disease and avoiding treatment directed specifically at triglyceride levels.

Andrew L. Avins, MD, MPH
Veterans Affairs Medical Center, San Francisco
University of California, San Francisco, School of Medicine
San Francisco, CA 94121

References

In response: Despite my attempts to portray the complexity of the issue and, therefore, make physicians aware that treatment was not based on data as good as those for LDL cholesterol, Dr. Avins obviously feels that my editorial was misdirected. In response to the major points of the letter: First, I omitted a very important recent paper from Hokanson and Austin (1) from my editorial. This meta-analysis convincingly demonstrated that triglyceride levels are independent predictors of future coronary artery disease in both men and women (1) and is more recent than either the 1989 or 1995 reports Dr. Avins mentioned. Second, the central goal of my editorial was to provide physicians with insight into the complex metabolic abnormalities in lipoprotein that are associated with hypertriglyceridemia. The interaction I mentioned supports the view that hypertriglyceridemia is part of a potent atherogenic dyslipidemic state. Finally, although Dr. Avins states that niacin, statins, and gemfibrozil are "associated with serious side effects, great expense, or elevated risk for conditions other than coronary heart disease," niacin is one of the least expensive medications available for the treatment of any disease and has been shown to reduce events and mortality (2). In addition, the statins have been shown to be safe and to markedly reduce events and mortality (3, 4). It is inappropriate and misleading to lump all of these drugs together in any blanket statement. Overall, I believe that my conclusions are based on both sound epidemiologic data and the availability of appropriate and efficacious therapies.

Henry N. Ginsberg, MD
College of Physicians & Surgeons of Columbia University
New York, NY 10027

References