Letters

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- Provide a self-addressed envelope if they want to be notified that the letter was received

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Stroke Prevention Guidelines

To the Editor: Matchar and colleagues (1) cite the Stroke Prevention in Atrial Fibrillation (SPAF) study analyses (2, 3) to support the claim that "patients younger than 60 years who have a normal echocardiogram and no risk factors have an extremely low risk for stroke (1% per year)." Because the prevalence of atrial fibrillation is strongly related to advanced patient age, this scheme suggests that fewer than 5% of approximately 2 million Americans with atrial fibrillation would be at low risk. We reported that patients of any age with atrial fibrillation and without specific clinical or echocardiographic risk factors have a relatively low risk for ischemic stroke (3). Such patients composed 26% of our study cohort and may represent an even larger portion of patients not enrolled in clinical trials (3).

Warfarin is more effective than aspirin in preventing ischemic stroke in patients with atrial fibrillation as a group (relative risk reduction, 47%; 95% CI, 26% to 61%) (4). We contend, however, that anticoagulation therapy can be deferred for many patients with atrial fibrillation and a low intrinsic risk for stroke. These patients may benefit little from anticoagulation when absolute rates are considered (Table 1). The clinical risk stratifiers derived by analyses of patients in the SPAF study given placebo have been validated in other cohorts (4, 5). Collaborative analysis of five primary prevention trials yielded similar, perhaps more generalizable, stratification variables. The ongoing SPAF III study is attempting to define additional subgroups of patients with atrial fibrillation who can be maintained at low risk with aspirin and for whom the need for lifelong anticoagulation may be reasonably postponed.

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References

In response: Recent clinical trials, including SPAF, have shown that anticoagulation with warfarin sodium can reduce the risk for stroke in patients with atrial fibrillation. As stated in our review, this relative risk reduction may not be worth the risks attendant to anticoagulation in patients in whom the absolute risk is small (1).

The crucial question is, who has a small absolute risk? The answer has been, and continues to be, a moving target. Indeed, since the submission of our manuscript, a pooled analysis by the Atrial Fibrillation Investigators has shown that persons with lone atrial fibrillation had a relatively low risk for stroke at any age (2). One caveat is that these data were derived not from a population-based survey but rather from the experience of vol-

Table 1. Risk Stratification in Atrial Fibrillation*

<table>
<thead>
<tr>
<th>Variables</th>
<th>SPAF-I Placebo</th>
<th>AFI Pooled Analysis</th>
<th>SPAF Echoanalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk variables</td>
<td>History of hypertension†</td>
<td>History of hypertension</td>
<td>History of hypertension</td>
</tr>
<tr>
<td></td>
<td>Previous stroke/TIA</td>
<td>Previous stroke/TIA</td>
<td>Previous stroke/TIA</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>Diabetes</td>
<td>Recent heart failure</td>
</tr>
<tr>
<td></td>
<td>Recent heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboembolic rate (95% CI), %</td>
<td>1.4/y (0.05 to 3.7)</td>
<td>1.0/y (0.3 to 3.1)</td>
<td>1.0/y (0.2 to 4.0)</td>
</tr>
<tr>
<td>Low-risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;7/y</td>
<td>&gt;5/y</td>
<td>&gt;6/y</td>
</tr>
<tr>
<td>High-risk variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients at low risk, %</td>
<td>38</td>
<td>15</td>
<td>26</td>
</tr>
</tbody>
</table>

* AFI = Atrial Fibrillation Investigators; LA = left atrial size by m-mode echocardiography; LV = left ventricular dysfunction by two-dimensional echocardiography; SPAF = Stroke Prevention in Atrial Fibrillation study; TIA = transient ischemic attack. Prospectively acquired data analyzed by multivariable techniques.
† History of hypertension includes patients with systolic blood pressure greater than 160 mm Hg.

1 February 1995 • Annals of Internal Medicine • Volume 122 • Number 3 235

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Omeprazole Therapy in Resistant Reflux Disease

To the Editor: In the recently published article on long-term omeprazole treatment (1), the authors attempted to explain the greater than expected elevation of plasma gastrin levels in 10 of 91 patients (11%) enrolled in the long-term omeprazole treatment study. We suggest that most, if not all, of these patients could be genetically determined to lack activity of the major enzyme responsible for metabolizing omeprazole, CYP 2C19. After 1 week of oral omeprazole (20 mg/d) given to both rapid and poor metabolizers, poor metabolizers showed a 2.9-fold greater half-life, a 4.8-fold greater maximum plasma concentration, and an 11.7-fold greater plasma area under the curve of omeprazole than did rapid metabolizers (2). Poor metabolizer frequency varies ethnically, with about 5% of whites (2) and as many as 22% of Asians (3) expressing the poor metabolizer phenotype. Rapid and poor metabolizers of omeprazole can be identified with a mephenytoin-phenotyping technique (4).

Omeprazole-induced hypergastrinemia and decreased vitamin B₁₂ absorption (5) are significant causes of concern for patients receiving long-term omeprazole therapy. Long-term omeprazole therapy would probably put persons with poor metabolism of omeprazole at increased risk for significant vitamin B₁₂ malabsorption, potentially leading to vitamin B₁₂ deficiency. We propose that poor metabolizers of omeprazole and S-mephenytoin are those at greatest risk for these and other long-term toxicities associated with omeprazole. Because poor metabolizers of omeprazole cannot readily be identified, we recommend that 1) long-term therapy with omeprazole be limited to the few persons with chronic erosive esophagitis and the Zollinger-Ellison syndrome who cannot be treated with other available therapies; 2) all patients receiving long-term omeprazole therapy have annual gastroscopy and B₁₂ measurements; 3) gastrin levels be measured after 3 months of omeprazole therapy; 4) persons with abnormally high gastrin levels or other omeprazole-related toxicities be phenotyped with mephenytoin; and 5) persons with abnormally high gastrin levels or other omeprazole-related toxicities be measured after 3 months of omeprazole therapy; analysis of pooled data from five randomized controlled trials. Arch Intern Med. 1994;154:1449-57.

References

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References
proved safety. Gastrin levels may vary sixfold in persons tested every 3 or 4 months during long-term omeprazole therapy, and yearly testing is as likely as thricely-yearly testing to identify patients with gastrin levels greater than 400 pg/mL (1). Graham's extraordinary recommendation that gastroscopies be done annually during omeprazole therapy was based on his observation of gastric mucosal nodularity in some patients (2). The nodules have since been shown to be mucosal cysts of no known clinical relevance (3).

Regardless of their rate of omeprazole metabolism, patients with high gastrin levels should have a trial of low-dose omeprazole or histamine-2 blockers because they may not need a high degree of gastric acid inhibition. Meanwhile, the effects of slow omeprazole metabolism on acid secretion, gastrin levels, and vitamin B12 absorption should be measured. Such pharmacokinetics data will be more useful than pharmacocinetics data in the creation of sound clinical recommendations.

Waldum and Brenna's observation that the maximum trophic effects of gastrin are reached at concentrations of less than 500 pH underscores the importance of an additional factor operating in patients with pernicious anemia and the Zollinger-Ellison syndrome and certain carcinoid tumors that is, hypergastrinemia appears to be necessary but not necessary and sufficient. The additional factor, possibly related to the multiple endocrine neoplasia type I gene in patients with the Zollinger-Ellison syndrome and to chronic inflammation in patients with pernicious anemia appears to trigger a transformation from ECL-cell hyperplasia to dysplasia and neoplasia.

To deny that safety concerns about omeprazole are diminishing is to ignore facts. Since the discovery of omeprazole-induced gastric carcinoid tumors in rats nearly a decade ago, regulatory agencies throughout the world have approved the use of omeprazole, including its long-term use in several countries. These developments reflect an increased understanding of the mechanisms of carcinoid formation, the absence of omeprazole-induced ECL-cell dysplasia or carcinoid tumors in long-term clinical trials, and the absence of carcinoid tumors in surveillance studies among the estimated 60 million patients who have been treated with omeprazole. It is also reassuring that gastric carcinoids are not known to occur years after gastric vagotomy, which causes gastric elevations greater than those resulting from omeprazole therapy (4).

Safety concerns persist, of course, and continued surveillance is necessary. Meanwhile, clinicians can use omeprazole to treat patients with recurrent esophagitis and can know that they are practicing within the experience of excellent long-term safety trials such as those of Lamberts and colleagues (5) and Klinkenberg-Knol and colleagues.

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References

In response: Drs. Waldum and Brenna express their concerns regarding omeprazole-induced hypergastrinemia. We have recommended continued follow-up of patients receiving long-term therapy with proton-pump inhibitors, particularly patients with high serum gastrin levels that showed enhanced progression toward atrophic gastritis. The significance of this finding remains unclear and requires further study. This follow-up strategy also applies to the risk for progression from hyperplasia to dysplasia of ECL cells.

Concerning the potential cause of food retention in patients with high gastrin levels, we have postulated that omeprazole might be responsible for the food retention caused by the decreased emptying rate of solid food in healthy volunteers (1-3). Another explanation might be decreased antral motility (4) and delayed gastric emptying caused by elevated serum gastrin levels. Vagal nerve damage might also be among the factors causing delayed gastric emptying in some of our patients.

Drs. Wright and Sarch suggest that the severe hypergastrinemia observed in 10 of 91 patients receiving long-term omeprazole therapy might be caused by a difference in metabolism of the drug. If their hypothesis is correct, a lower dose of omeprazole should be needed in these patients to achieve remission. However, we did not observe a decreased need for the drug. In contrast, these patients experienced frequent recurrences during maintenance treatment with omeprazole (20 mg/d or 40 mg/d).

In our opinion, the main cause of this severe hypergastrinemia is delayed gastric emptying.

Profound acid inhibition may interfere with the absorption of certain nutrients such as iron and cobalamin (5). However, although the resorption of protein-bound cobalamin was found to decrease during omeprazole treatment, no changes in serum cobalamin levels were detected during continuous maintenance therapy that lasted as long as 4 years (5). Similarly, no changes in several other metabolic measurements were found during long-term treatment.

We agree that conscientious behavior by physicians in prescribing proton-pump inhibitors, particularly in young patients, is still required.

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Omeprazole, Serum Gastrin, and Gastric Acid Suppression

To the Editor: It is well known that the decrease in gastric activity caused by omeprazole results in increased serum gastrin levels. We asked whether a precise relation exists between fasting serum gastrin levels and gastric acid suppression in patients receiving omeprazole. If such a relation exists, physicians could obtain fasting serum gastrin levels from their patients receiving omeprazole as a simple measure of the degree of gastric acid suppression. We used ambulatory intragastric pH monitoring to assess gastric acid suppression in 45 patients with gastroesophageal reflux who were receiving different doses of omeprazole. The pH probe was placed with the antimony electrode in the...
gastric fundus, 10 cm below the manometrically located lower esophageal sphincter. Monitoring was accomplished using a battery-powered Mark 3 Digitrapper (Synetec Medical, Inc., Irving, Texas). Serum gastrin was drawn after an overnight fast, immediately after placement of the pH probe, and at the start of 24-hour monitoring.

Figure 1 shows the relation between the total percentage of time the intragastric pH remained less than 4.0 over the entire 24-hour period and fasting serum gastrin levels, obtained on the testing day and expressed in pg/mL for patients receiving daily omeprazole doses of 20, 40, and 80 mg. Regression analysis shows a poor correlation (r = 0.04) when the collective fasting serum gastrin levels are compared with the total percentage of time the intragastric pH remained less than 4.0 in the 45 patients receiving omeprazole therapy. Many patients receiving various omeprazole doses had fasting gastrin values in the normal range (<100 pg/mL).

To determine whether this relation was affected by the omeprazole dose, we also compared the fasting serum gastrin level with the total percentage of time the intragastric pH remained less than 4.0 on individual doses. A poor correlation was consistently found at all dose levels.

We conclude that serum gastrin levels do not reliably predict the degree of gastric acid suppression in patients receiving omeprazole.

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Urinary Tract Infection with Enterococcus faecalis

To the Editor: Fraimow and colleagues (1) report the first instance of a vancomycin-dependent organism but not the first example of a clinical isolate that required an antimicrobial agent for growth. In 1955, Finland (2) reviewed reports of clinical isolates, including tubercle bacilli, that needed streptomycin for growth. In one report, the condition of a patient with a streptomycin-dependent organism but not the first to report a clinical isolate that required an antimicrobial agent for growth (1). In addition to being a well-described laboratory phenomenon, streptomycin dependence has also been reported in several clinical isolates (2). Of note, many of these antibiotic-dependent strains were also isolated from the urinary tract, an environment in which a large inoculum of organisms may be continuously exposed to high antibiotic concentrations for prolonged periods and in which an antibiotic-resistant organism may take the “next” evolutionary step toward the development of antibiotic dependence. As Dr. Jacoby has observed, various antibiotic-dependent strains have been isolated in the laboratory. In addition to their novelty, such strains can also be powerful tools for studying the basic mechanisms of antibiotic action and resistance (3). It is perhaps not surprising that antibiotics can serve as positive regulators of bacterial growth, given that most of these compounds are natural products of soil organisms and that they may have once functioned as primitive cellular effector molecules (4, 5). We agree that the prevalence of antibiotic-dependent bacteria is unknown and will remain so until we begin to search for such strains in the appropriate clinical settings.

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References

Correction: Incorrect Formula

A recent article on survival in primary pulmonary hypertension (1) contained an error in the formula for predicting survival. The correct formula is as follows:

\[
P(t) = \frac{H(t)}{H(0)^{\alpha (y,z)}} = \frac{[0.88 - 0.14t + 0.01t^2]}{[0.88 - 0.14t + 0.01t^2]}\]

where

- \(x\) = mean pulmonary artery pressure
- \(y\) = mean right atrial pressure
- \(z\) = cardiac index

Reference