

INTERNAL MEDICINE ALERT[®]

A twice-monthly update of developments in internal and family medicine

Providing Evidence-based
Clinical Information for 23 Years

American Health Consultants Home Page—<http://www.ahcpub.com>

CME for Physicians—<http://www.cmeweb.com>

EDITOR

Stephen A. Brunton, MD
Clinical Professor,
University of California Irvine

ASSOCIATE EDITORS

James Chan, PharmD, PhD
Pharmacy Quality and
Outcomes Manager, Kaiser
Permanente, Oakland, CA

William T. Elliott, MD, FACP
Chair, Formulary Committee,
Northern California Kaiser
Permanente; Asst. Clinical
Professor of Medicine, University
of California-San Francisco

Mary Elina Ferris, MD
Associate Clinical Professor,
Loma Linda University
Clinical Associate Professor
University of Southern California

Ken Grauer, MD
Professor, Assistant Director,
Family Practice Residency
Program, University of Florida
ACLS Affiliate Faculty for Florida

Ralph R. Hall, MD, FACP
Emeritus Professor of Medicine
University of Missouri-
Kansas City School of Medicine

**Harold L. Karpman, MD,
FACC, FACP**
Clinical Professor of Medicine,
UCLA School of Medicine

Louis Kuritzky, MD
Clinical Assistant Professor,
University of Florida,
Gainesville

Martin Lipsky, MD
Professor and Chair,
Department of Family Medicine,
Northwestern University
Medical School, Chicago, IL

David Ost, MD
Assistant Professor of Medicine,
NYU School of Medicine,
Director of Interventional
Pulmonology, Division of
Pulmonary and Critical Care
Medicine, Northshore University
Hospital, Manhasset, NY

Barbara A. Phillips, MD, MSPH
Professor of Medicine,
University of Kentucky;
Director, Sleep Disorders
Center, Samaritan Hospital,
Lexington, KY

Michael K. Rees, MD, MPH
Senior Associate in Medicine,
Beth Israel Deaconess
Medical Center,
Instructor in Medicine,
Harvard Medical School
Brookline, MA

**Malcolm Robinson, MD,
FACP, FACC**
Medical Director, Oklahoma
Foundation for Digestive
Research; Clinical Professor of
Medicine, University of Okla-
homa College of Medicine
Oklahoma City, OK

Kamaljit Sethi, MD, FACP
Clinical Professor of Medicine,
Georgetown University School of
Medicine; Attending Physician,
Providence Hospital,
Washington, DC

**Sheldon L. Spector, MD,
FACP, FAAA, FACA**
Clinical Professor, Department
of Medicine, UCLA School of
Medicine, Los Angeles

Hope for Oenophiles: Smart People Drink Wine, not Beer

ABSTRACT & COMMENTARY

Synopsis: *Danish people who drink only wine have higher IQs, socioeconomic status, and educational levels than do those who drink only beer. Further, they score better on tests of personality and are less likely to smoke cigarettes. These differences may explain some of the health benefits of wine.*

Source: Mortensen EL, et al. *Arch Intern Med.* 2001;161:1844-1848.

This paper is the result of an interesting collaboration between the Danish Epidemiology Science Center in Copenhagen and the Kinsey Institute for Research in Sex, Gender, and Reproduction in Bloomington, Ind. The purpose of this study was to determine if personality and behavior factors explain the apparent health benefits enjoyed by wine drinkers. Mortensen and colleagues compared socioeconomic status, education, IQ, personality, psychiatric symptoms, and health-related behaviors between beer and wine drinkers in Denmark. The study population was a subset of a larger sample that was recruited to study the effects of prenatal exposure to prescribed medications.

There were 693 subjects (330 women) aged 29-34 years. Participants were divided into 4 groups based on beverage drinking in the past week: nondrinkers of either beer or wine (n = 169, 116 women), wine only (n = 94, 73 women), beer only (n = 90, 67 men), both beer and wine (n = 340, 222 men). Consumption of liquor in this group was rare; median consumption was 0-1 drinks/week, regardless of beer or wine consumption. Linear regression revealed an interaction between beer and wine only for women's parental educational level. There were many interactions between alcohol choice and sex, so data were analyzed separately by gender.

For both men and women, wine drinking was associated with higher scores in parental social status, parental educational level, and subject's educational and social status. For both sexes, beer drinking was associated with lower scores on IQ scales. This was most dramatic for males: "pure" wine drinking men had average IQs of 113.2, compared with 95.2 for "pure" beer-drinking men.

INSIDE

*Normaliza-
tion of INR*
page 147

*Evaluating
patients with
syncope*
page 147

**Pharmacolo-
gy Update:**
*Ribavirin—A
new option for
the treatment
of hepatitis C*
page 149

**Clinical
Briefs:**
*Severe
pulmonary
embolism
associated
with air
travel*
page 151

Volume 23 • Number 19 • October 15, 2001 • Pages 145-152

NOW AVAILABLE ONLINE!
Go to www.internalmedicinealert.com for access.

Measures of personality also showed significant differences between beer and wine drinkers. Scores on the Million Clinical Multiaxial Inventory were lower (healthier) for pure wine drinkers, with pure beer drinkers having the highest scores. Beer drinking was associated with a higher prevalence of risk drinking, smoking, and illicit drug use, and wine drinking was associated with a lower prevalence of smoking. Total alcohol consumption was larger for beer drinkers. On most measures, abstinence was associated with a less desirable score than was wine consumption, but with a better score than pure beer consumption.

■ COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

A large body of evidence demonstrates that wine drinkers have a lower risk of coronary heart disease, stroke, upper GI cancer, lung cancer, hip fracture, and

all-cause mortality compared with those who are abstinent or who drink beer or liquor.¹⁻⁷ The current study makes a case for attributing the better health of wine drinkers to their underlying personalities, intelligence, and socioeconomic status, not to any particular health benefit of wine. There are a couple of issues to consider in sorting out the significance of this finding. The first is that alcohol in general is associated with reduced cardiovascular mortality, probably because of ethanol-induced elevations in high density lipoproteins (HDLs)⁸ and lowering of platelet aggregation.⁹ The second is that, much as wine drinkers appear healthier than beer drinkers, there is some evidence that red wine drinkers may benefit more than white wine drinkers. Red wine contains antioxidants such as resveratrol, which has been shown to inhibit the expression of tissue factor and cytokines, which are associated with thrombogenesis.¹⁰ Unable to find any head-to-head trials about the health benefits of red vs. white wines, I consulted an expert: my brother-in-law. Dr. Charles Orr is a cardiologist, oenophile, and scholar, with whom I have shared more than a few glasses of wine. Although there do not appear to be epidemiologic studies directly comparing health benefits of red and white wine, there is substantial in vitro evidence that red wine contains more antioxidant and antiplatelet activity than does white wine.^{11,12} My consultant also pointed out what should have been obvious to me: although this study indicates that wine drinkers are smarter, better educated, etc, etc than beer drinkers, it does not prove causality.¹³ It may be that, contrary to Mortensen et al's assertion that personality characteristics dictate beverage choice, the converse is true. Maybe drinking wine makes us smarter. ♦

References

1. Rimm EB, et al. *Lancet*. 1991;338:464-468.
2. Gronbaek M, et al. *J Epidemiol Community Health*. 1999;53:721-724.
3. Truelsen T, et al. *Stroke*. 1998;29:2467-2472.
4. Gronbaek M, et al. *BMJ*. 1998;317:844-847.
5. Prescott E, et al. *Am J Epidemiol*. 1999;149:463-467.
6. Hoidrup S, et al. *Am J Epidemiol*. 1999;149:993-1001.
7. Gronbaek M, et al. *BMJ*. 1995;310:1165-1169.
8. Gaziano JM, et al. *N Engl J Med*. 1993;329:1829-1834.
9. Elwood PC, et al. *Circulation*. 1991;83:38-44.
10. Pendurthi U, et al. *Arterioscler Thromb Vasc Biol*. 1999;19:419-426.
11. Araya J, et al. *Br J Nutr*. 2001;86:189-195.
12. Ivanov V, et al. *J Agric Food Chem*. 2001;49:4442-4449.
13. Personal communication. Charles M. Orr, MD, September 21, 2001.

Internal Medicine Alert, ISSN 0195-315X, is published twice monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER:

Donald R. Johnston.

EDITORIAL GROUP HEAD: Glen Harris.

MARKETING PRODUCT MANAGER:

Schandale Kornegay.

MANAGING EDITOR: Robin Mason.

ASSOCIATE MANAGING EDITOR: Neill Larmore.

SENIOR COPY EDITOR: Robert Kimball.

GST Registration Number: R128870672.

Periodical postage paid at Atlanta, GA.

POSTMASTER: Send address changes to *Internal*

Medicine Alert, P.O. Box 740059, Atlanta, GA 30374.

Copyright © 2001 by American Health Consultants. All rights reserved. No part of this newsletter may be reproduced in any form or incorporated into any information-retrieval system without the written permission of the copyright owner.

Back issues: \$18. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

AMERICAN HEALTH CONSULTANTS

THOMSON HEALTHCARE

Questions & Comments

Please call **Robin Mason**, Managing Editor, at (404) 262-5517 (e-mail: robin.mason@ahcpub.com) or **Neill Larmore**, Associate Managing Editor, at (404) 262-5480 (e-mail: neill.larmore@ahcpub.com) between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Subscriber Information

Customer Service: 1-800-688-2421.

Customer Service E-Mail: customerservice@ahcpub.com

Editorial E-Mail: neill.larmore@ahcpub.com

World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States

\$269 per year (Student/Resident rate: \$110).

Multiple Copies

1-9 additional copies: \$179 each; 10 or more copies: \$175 each.

Canada

Add 7% GST and \$30 shipping

Elsewhere

Add \$30 shipping

Accreditation

American Health Consultants (AHC) designates this continuing medical education (CME) activity for up to 40 hours in Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians. This CME activity was planned and produced in accordance with the ACCME Essentials.

Internal Medicine Alert has been approved by the American Academy of Family Physicians as having educational content acceptable for prescribed credit hours. Term of approval covers issues published within one year from the beginning distribution date of January 1, 2001. This volume has been approved for up to 40 prescribed credit hours. Credit may be claimed for one year from the date of this issue.

The program is also approved by the American Osteopathic Association for 40 Category 2B credit hours.

For CME credit, add \$75.

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Brunton is a consultant for Andrx, Reliant, and AstraZeneca and serves on the speaker's bureau of Janssen, Schering, Aventis and AstraZeneca. Dr. Hall is a stockholder of GlaxoSmithKline. Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3-M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim. Dr. Lipsky is a consultant for and is on the speaker's bureau of Aventis and AstraZeneca. Dr. Ost is on the speaker's bureau of Merck, Roche, and Boehringer Ingelheim and does research for the American Lung Association. Dr. Phillips serves on the speaker's bureau of Cephalon, Boehringer Ingelheim, Wyeth-Ayerst, and GlaxoSmithKline and is a consultant for Boehringer Ingelheim. Dr. Robinson serves as a consultant for Pfizer, Janssen, Wyeth-Ayerst, AstraZeneca, Salix, Reliant, Solvay, TAP, GlaxoSmithKline, and Novartis. Dr. Sethi is on the speaker's bureau of Bristol-Myers Squibb and does research for Bristol-Myers Squibb and Ortho Biotech. Drs. Chan, Elliott, Ferris, Grauer, Karpman, Wilke, and Rees report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

Normalization of INR

ABSTRACTS & COMMENTARY

Synopsis: *The information from this study may prove helpful in deciding whom to give vitamin K, what dose to provide, and how soon to perform a follow-up INR.*

Sources: Hylek EM, et al. *Ann Intern Med.* 2001;135:393-400; Bussey HI. *Ann Intern Med.* 2001;135:460-462.

Hylek and colleagues ask the question, what are the patient-specific factors that influence the rate of normalization of the international normalized ratio (INR) after interruption of warfarin therapy? Knowing which patients can be predicted to normalize rapidly might avoid the administration of vitamin K, which has the potential of overcorrection of INR, warfarin resistance, and increased risk of thromboembolism. On the other hand, it will be of help in identifying those patients who are at risk for prolonged exposure to excessive anticoagulation (and, therefore, hemorrhage) and require more aggressive intervention.

Hylek and colleagues performed a retrospective study of patients who had been taking warfarin for more than 60 days and whose index INR was greater than 6.0. During the period of August 1993 through September 1998, 633 patients were studied. Variables included: recently started medications, intercurrent illness, decrease in oral intake, confusion about dose or nonadherence, errors in warfarin prescription, hospitalization within 30 days, report of increased alcohol intake, decompensated heart failure within 14 days of the index INR, and active cancer (chemotherapy or evidence of metastatic disease). The mean age of patients was 69 years (range, 25-95 years) and 55% were female. Nearly 80% had taken warfarin for more than 1 year, and 90% had less than a 10% change in warfarin dose over the previous 2 INR measurements.

Hylek et al report that patients whose INR remained 4 or greater on day 2 after the last dose of warfarin were more likely to be older, to be taking a lower maintenance dose of warfarin, and to have had a higher index INR (INR of 8 or higher). Other parameters associated with an INR of 4 or greater on day 2 included decompensated congestive heart failure, active cancer, and recent use of a medication known to potentiate warfarin. Too few patients reported alcohol use to allow meaningful assessment.

■ COMMENT BY MICHAEL K. REES, MD, MPH

The information in this paper can be used when faced

with that thorny decision: “Can I wait it out or should I give the patient vitamin K?” Hylek et al found that the rate of decay of INR was a function of age: the odds of having an INR of 4 or greater increased by 18% for each decade of age. That the rate of decay of INR is slower in patients who require low doses of warfarin to maintain INR in therapeutic range seems logical, as does the finding that the higher the index INR, the more likely that it will not have fallen below 4 on day 2. The observation that recent onset of decompensated heart failure is a risk is important. It certainly means that we have to use warfarin with great care here, and the finding of a high INR in an otherwise stable cardiac patient might be a warning to look for onset of CHF. The patient with “active cancer” also requires close monitoring.

In an accompanying editorial, Bussey makes the following comments: “Because the study is retrospective, there was no opportunity to repeat the Index INR to ensure it was not in error, which is important because 10-20% of laboratory INR measurements are erroneous, and half are higher than 4.5. Nevertheless, until data from prospective studies are available, this information may prove helpful in deciding whom to give vitamin K, what dose to provide, and how soon to perform a follow-up INR.” Bussey suggests the following: 1) do not give vitamin K subcutaneously because it is ineffective in some patients; 2) the oral route is reliable; 3) limit the oral dose of vitamin K to 2.5 mg if the INR is between 6 and 10 or 5 mg if the INR is greater than 10. If there is concern that correction of INR may overshoot, measure INR 24 hours (rather than 48 hours) after vitamin K, which will allow warfarin to be restarted—if appropriate. If vitamin K is given intravenously, usually 0.5 mg is effective, and infuse at a rate of less than 1 mg/min. ❖

Evaluating Patients with Syncope

ABSTRACT & COMMENTARY

Synopsis: *A good history and physical examination, plus basic laboratory, ECG, carotid massage, and testing for hypotension can identify 3 of every 4 causes of syncope.*

Source: Sarasin FP, et al. *Am J Med.* 2001;111:177-184.

There is no “gold standard” to diagnose syncope, since it is a symptom of several diseases. This

study set out to measure the diagnostic yield of a pre-defined, sequential syncope protocol in a community-based group of patients.

Over a 21-month period, Sarasin and colleagues evaluated and prospectively followed all 788 patients who presented to the emergency department of the major primary and tertiary care hospital in their region with syncope. After excluding 138 patients who either did not complete the protocol (115) or who refused to participate (23), they enrolled 650 patients in the study. They defined syncope as “a sudden, transient loss of consciousness with an inability to maintain postural tone and spontaneous recovery.” The patients ranged in age from 18 to 93 years old (mean age 60). Males made up 48% of the group. Thirty-six percent of these patients had known comorbid conditions including coronary artery disease, previous myocardial infarction, heart failure, hypertension, diabetes mellitus, peripheral vascular disease, and chronic obstructive pulmonary disease. All patients had an initial evaluation consisting of a history and physical examination using a standardized protocol, plus hematocrit, serum creatine kinase, serum glucose, electrocardiogram (ECG), carotid massage, and orthostatic blood pressures and pulses. Afterwards, they were divided into 3 groups: those in whom a diagnosis was strongly suspected (446); those in whom a diagnosis was suspected, but needed confirmation (67); and those in whom the diagnosis was unclear (137).

Sarasin et al used predefined criteria to assign the causes of syncope, including attempts to reproduce the symptoms when possible. The causes of syncope were divided into 2 groups, cardiac and noncardiac.

In the first group, history and physical examination yielded a diagnosis in 245. The most common abnormality was vasovagal syncope (37%). Orthostatic hypotension represented almost one quarter of the diagnoses. These patients had drug-related hypotension (most often associated with angiotensin-converting enzyme [ACE] inhibitors), hypovolemia, postprandial hypotension, or idiopathic hypotension. Laboratory evaluation picked up gastrointestinal hemorrhage in 2 patients and hypoglycemia in 3.

In the second group, a cause of syncope was confirmed by selected diagnostic testing in 49. The suspected causes were seizure, stroke/TIA, pulmonary embolism, aortic stenosis, arrhythmia, mastocytosis, and subdural hematoma. The diagnostic procedures used were electroencephalogram (EEG), computed tomography (CT), lower limb venous compression ultrasound, plasma D-dimer quantification, lung scan, echocardiogram, Holter monitor, and consultation.

The number of patients with a confirmed diagnosis then was 495.

When the 18 patients without a diagnosis in group 2 were added to the third group, there were 155 patients with no cause for syncope after initial clinical evaluation. Of these, 33 pursued no further investigations, either because the patients refused or were in poor health or for logistical reasons. Of the remaining 122 patients, a diagnosis was confirmed in 30 after extensive work-up. All 30 had abnormal baseline ECGs. The work-up included 24-hour Holter monitoring, ambulatory loop ECG recording, echocardiography, tilt-table testing, and electrophysiological (EP) studies. Interestingly, although the echocardiograms revealed abnormalities in some patients, none of the abnormalities were considered pertinent to syncope. Holter monitoring, ambulatory loop recording, tilt-table testing, and EP testing helped establish diagnoses in 9, 3, 11, and 7 patients, respectively. This increased the number of patients with a diagnosis to 525 (see Table).

Table	
Causes of Syncope	
Causes of syncope	Number (%)
Vasovagal	242 (37)
Orthostatic hypotension	158 (24)
Unknown	92 (14)
Arrhythmias	44 (7)
Incomplete evaluation	33 (5)
Neurologic	30 (5)
Psychiatric	11 (1.5)
Other noncardiac causes	9 (1.5)
Acute coronary syndrome	9 (1.5)
Aortic stenosis	8 (1.2)
Pulmonary embolism	8 (1.2)

These patients were followed for 18 months, during which 55 died. Patients with a cardiac cause of syncope were more likely to die. Also during this period, 95 patients (15%) had 1 or more recurrences of syncope.

■ COMMENT BY ALLAN J. WILKE, MD

Syncope, a short-lived loss of consciousness, accounts for 3% of all emergency room visits (1.1% in this study). It is the result of a bewildering and disparate number of diseases, some of them potentially life threatening, some of them with specific therapies. Its transitory nature, while ultimately a blessing for the patient, makes diagnosis difficult. It is not amenable to our calls to “come back when you have it again.” Unless your

patient is attached to telemetry or some cardiac event monitor when syncope occurs, the diagnosis is very much an educated guess, but that's okay. This study's value is in its reassurance that we can come to a diagnosis, more often than not, with tools that are readily available to anyone practicing adult medicine.

The study does raise some methodological questions. First, this study was done in Geneva, Switzerland. Does Sarasin et al's study group resemble the patients I see with syncope? Maybe. Although they do not provide ethnic or racial breakdowns, I assume that their patients were predominantly Swiss and probably overwhelmingly Caucasian. Second, is their definition of syncope too broad? For instance, a seizure might look like "a sudden, transient loss of consciousness with an inability to maintain postural tone and spontaneous recovery." However, I would argue that by keeping the definition broad and then assigning a diagnosis (such as seizure) keeps in perspective the reality that, at first, we do not always know what disease has caused the symptom.

The diagnostic yield of an extensive workup (30/155 or 19%) is disappointing. I would like to see a cost analysis of this. It may make sense to limit an extensive work-up to that patient who has an abnormal ECG at baseline. ❖

Dr. Wilke is an Assistant Professor of Family Medicine, Medical College of Ohio, Toledo, Ohio.

Pharmacology Update

Ribavirin—A New Option for the Treatment of Hepatitis C

*By William T. Elliott, MD, FACP,
and James Chan, PharmD, PhD*

The fda recently approved a "stand-alone package" of ribavirin capsules for the treatment of hepatitis C. Ribavirin is used in combination with interferon—either interferon alfa-2b or peginterferon alfa-2b. In 1998 the FDA approved a combination package of ribavirin and interferon alfa-2b that has been marketed under the trade name Rebetron. With the recent approval of a pegylated interferon alpha (PEG-Intron, Schering) and another on the way (Pegasys-Roche), ribavirin as a stand-alone product allows the flexibility to use these drugs in combination.

Indication

Ribavirin is indicated for use in combination with interferon alfa-2b (Intron A) for the treatment of chronic hepatitis C in adult patients with compensated liver disease previously untreated with alpha interferon or who have relapse after interferon therapy.¹ It is also indicated in combination with peginterferon alfa-2b (PEG-Intron) for the treatment of chronic hepatitis C in patients with compensated liver disease who are naïve to interferon alpha therapy.²

Dosage

The recommended dose of ribavirin with interferon alfa-2b is based on body weight. For patients < 75 kg the dose is 400 mg (2 · 200 mg) in the **am** and 600 mg (3 · 200 mg) in the **pm**. For patients > 75 kg, the dose is 600 mg (3 · 200 mg) in the **am** and **pm**. This is administered with 3 million IU of interferon alfa-2b (Intron A) 3 times weekly. In patients with a history of stable cardiovascular disease, a permanent dose reduction is needed if the hemoglobin decreases by 2 g/dL or greater during any 4-week period. Ribavirin should be discontinued if the hemoglobin remains below 12 g/dL after 4 weeks of a reduced dose. In patients with no cardiac history, the dose should be reduced to 600 mg daily (200 mg **am** and 400 mg **pm**) if hemoglobin falls below 10 g/dL and discontinued if it falls below 8.5 mg/dL.¹

In combination with peginterferon (1.5 mg/kg/wk), the recommended dose is 800 mg in 2 divided doses (with breakfast and dinner). If hemoglobin drops below 10 mg/dL, but not below 8.5 mg/dL, the dose should be reduced by 200 mg/d.² In those with a history of stable cardiovascular disease, the dose of peginterferon should be reduced by half and the dose of ribavirin by 200 mg/d if there is a > 2 g/dL decrease in hemoglobin in any 4-week period, and discontinued if Hgb is < 12 g/dL. Ribavirin should be discontinued if there is significant decrease in WBC, neutrophils, or platelets.²

Treatment is generally 24-48 weeks for treatment-naïve patients and 24 weeks for treatment-relapse patients.

Ribavirin is supplied as 200-mg capsules in packages of 84. The bottles should be stored at 25°C or 77°F.

Potential Advantages

The approval of the "stand alone" ribavirin provides more dosing flexibility in tailoring individualized therapy for those patients requiring dosage reduction as well as allowing use with peginterferon. In the clinical trials, about 26% of patients required modification in the dose of ribavirin. These included dose reduction or discontinuation. The combination package (Rebetron) contains a

week's supply of ribavirin (35 or 42 capsules) and does not allow for the flexibility of dose reduction in patients with anemia associated with ribavirin therapy.

Potential Disadvantages

Ribavirin is not effective as monotherapy for hepatitis C. Hemolytic anemia, which occurs in about 10% of patients, is the primary adverse effect of ribavirin.¹ The drug can also potentiate the neutropenia induced by interferon alpha.² Ribavirin should not be used in pregnant patients or those with a creatinine clearance < 50 mg/min.

Comments

The combination of ribavirin and interferon alfa-2b has been approved for the treatment of patients who have relapsed following interferon alfa-2b therapy as well as those naïve to treatment. The combination has been reported to be more effective than interferon alone in both relapsing as well as naïve patients.^{1,3,4,7} Ribavirin was recently approved for use in combination with peginterferon alfa-2b (PEG-intron) which is a conjugate of monomethoxy polyethylene glycol (PEG) with recombinant interferon alfa-2b. The pegylated interferon permits a more convenient once-weekly dosing. In interferon treatment-naïve patients, the combination of ribavirin (800 mg daily) plus peginterferon (1.5 µg/kg week) produced a better overall response (undetectable virus in the serum in 24 weeks) than ribavirin (1000 or 1200 mg) plus interferon 3 MIU 3 times a week (52% vs 46%, respectively). The difference was seen in genotype 1 hepatitis C compared to genotypes 2-6.^{2,6} A recent report of a 24-week interim analysis suggests that ribavirin/peginterferon may be effective in patients who have previously failed on other interferon therapy.⁵

Clinical Implications

It is estimated that about 4 million Americans are chronically infected with hepatitis C and it is the leading reason for liver transplantation in this country. The combination of ribavirin and interferon is currently considered the standard of care. The approval of "stand alone" ribavirin permits its use with peginterferon and also allows for more flexibility in dosage modification due to adverse effects. As more data are published, peginterferon may become the standard interferon. Schering has agreed to conduct several postmarketing studies including the comparison of weight-adjusted doses of ribavirin with the currently approved fixed dose which is underway. Data suggest that body weight is an important predictor of response to interferon.⁶ Rebetol is expected to

be available in November and a combination PEG-Intron/Rebetol product is also pending. ❖

References

1. Rebetol Product Information. Schering Corporation. July 2001.
2. PEG-Intron Product Information. Schering Corporation. August 2001.
3. Mereno-Monteagudo, et al. *Aliment Pharmacol Ther.* 1998;12(8):717-723.
4. Reichard O, et al. *Lancet.* 1998;351:83-87.
5. Jacobson I, et al. *Digestive Disease Week 2001.* May 20-23, 2001. Atlanta, GA. Abstract #1964.
6. Manns MP, et al. *Lancet.* 2001;358:958-965.
7. Poynard T, et al. *Lancet.* 1998;352:1426-1432.

CME Questions

25. As compared with people who drink only beer, people who drink only wine have:
 - a. higher IQs, lower smoking prevalence rates, better scores on personality tests, and higher socioeconomic status.
 - b. lower IQs, lower smoking prevalence rates, better scores on personality tests, and higher socioeconomic status.
 - c. higher IQs, higher smoking prevalence rates, better scores on personality tests, and higher socioeconomic status.
 - d. higher IQs, lower smoking prevalence rates, poorer scores on personality tests, and higher socioeconomic status.
 - e. higher IQs, lower smoking prevalence rates, better scores on personality tests, but lower socioeconomic status.
26. The most common cause of syncope is:
 - a. aortic stenosis.
 - b. vasovagal.
 - c. ventricular tachycardia.
 - d. orthostatic hypotension.
 - e. seizure disorder.
27. The patient has been taking warfarin for more than 1 year. To maintain the INR within the range of 1.8-2.4 IU, the patient has required a warfarin dose of between 1 and 2 mg/d. Today the INR is reported to be 7 IU. Which one of the following statements is correct?
 - a. Because the patient requires only a low dose of warfarin to maintain INR in the desired therapeutic range, it is likely that the rate of decline of INR will be rapid.
 - b. Because the patient requires only a low dose of warfarin to maintain INR in the desired therapeutic range, it is likely that the rate of decline of INR will be slow.
 - c. All of the above
 - d. None of the above
28. Which one of the following is *not* true about ribavirin?
 - a. It is indicated for the treatment of hepatitis C only in combination with interferon.
 - b. Hemolytic anemia is the primary adverse reaction to the drug.
 - c. Data suggest that ribavirin/peg-interferon may have some benefits over ribavirin-interferon.
 - d. Treatment regimens are generally 12 weeks.

By Louis Kuritzky, MD

Severe Pulmonary Embolism Associated with Air Travel

The relative immobility associated with air travel has long been suspected as causative in some cases of pulmonary embolism (PE), but until the current report, definitive data did not exist to prove the relationship. To study the relatedness of air travel and PE, Lapostolle and colleagues reviewed data from 135 million passengers arriving at Paris' Charles de Gaulle Airport from 1993-2000. In this population, 56 cases of PE were confirmed; case confirmation required appropriate clinical symptomatology coupled with a positive ventilation-perfusion scan, pulmonary angiogram, or high-resolution helical CT angiography. PE clinical syndromes were included in the study analysis only if they occurred within 1 hour of landing at the airport.

There was a direct and linear relationship between the frequency of PE and the distance traveled. The incidence of PE in passengers traveling less than 3100 miles was more than 100-fold less common than that among passengers traveling more than 3100 miles. For persons traveling more than 6200 miles, the incidence of PE was 3-fold greater still than those traveling more than 3100 miles.

PE after long air travel remains extremely uncommon. Lapostolle et al have demonstrated that, as intuition would anticipate, longer travel increases PE risk. Though not studied in this population, they suggest that simple measures such as adequate hydration, position change, or support stockings might reduce risk for PE. ❖

Lapostolle F, et al. *N Engl J Med.* 2001;345:779-783.

Effect of Levodopa in Combination with Physiotherapy on Functional Motor Recovery After Stroke

In addition to the ominous impact of stroke mortality in our nation (no. 3 cause of death), many at-risk individuals view the specter of poststroke impairment as worse than death. Animal studies have demonstrated that use of amphetamines in poststroke models is additive to physiotherapy in benefit for motor rehabilitation. The mechanism by which amphetamines enhance motor recovery is uncertain, the norepinephrine (NE) is the proposed candidate mediator.

Because of the cardiovascular toxicity of NE, it is unfeasible to administer NE poststroke. Another way to augment central nervous system NE is to administer levodopa, which is converted in the brain and metabolized in sparing amounts (about 5%) to NE. Scheidtmann and colleagues studied the effect of levodopa 100 mg/d as a single dose for 3 weeks vs. placebo in 53 ischemic stroke patients. All patients received traditional physiotherapy. Effects were measured by the Rivermead motor assessment (RMA) tool.

Administration of levodopa was associated with a statistically significant improvement in RMA over physiotherapy alone. At the second study observation point (3 weeks after active drug cessation), levodopa recipients still maintained an advantage over the placebo group. No patient experienced problematic side effects.

Levodopa appears to enhance the motor rehabilitation response to traditional physiotherapy. ❖

Scheidtmann K, et al. *Lancet.* 2001; 358:787-790.

Antibiotic Treatment of Adults with Sore Throat by Community Primary Care Physicians: A National Survey

Despite the fact that a diversity of suggested management plans for acute upper respiratory infections abounds, clinicians often use methods that reflect practice contrary to such guidance. Linder and Stafford propose that in cases of sore throat, the only bacteria that merits treatment is Group A beta-hemolytic streptococci (GABHS), for which first-line treatment recommendations generally include penicillin and erythromycin.

Linder and Stafford performed a retrospective analysis of 2244 adult primary care visits for sore throat over a 10-year period (1989-1999). Almost three-fourths of patients received antibiotic treatment, though it has been repeatedly demonstrated that the majority of adult pharyngitis cases are viral. Additionally, less than one-third of the antibiotic prescriptions were for penicillin or erythromycin.

Over the 10-year study period, use of nonrecommended antibiotics actually increased. On the other hand, in the most recent year surveyed, overall antibiotic prescribing was reduced by almost one-third, though there was no diminution of nonrecommended antibiotic use, most common of which was prescription of aminopenicillins. They have demonstrated that community-based primary care physicians commonly overprescribe antibiotics, and often choose agents which are not traditionally recommended as first-line. ❖

Linder JA, Stafford RS. *JAMA.* 2001; 286:1181-1186.

How Many Chambers?

By Ken Grauer, MD

Figure. 12-lead ECG obtained from a 49-year-old man with hypertension, a history of alcohol abuse, and progressive dyspnea. What might this echocardiogram show?

Clinical Scenario: The 12-lead ECG shown in the Figure was obtained from a 49-year-old African American man with a history of hypertension, alcohol abuse, and progressively increasing dyspnea. What might his echocardiogram show? How many cardiac chambers are likely to be enlarged?

Interpretation: The rhythm is sinus tachycardia at a rate of about 115 beats/minute. The PR and QRS intervals are normal. The mean QRS axis is rightward, as suggested by the negative QRS complex in lead I. Batrial enlargement is suggested by the presence of tall, peaked P waves in the inferior leads (right atrial enlargement [RAE]) and by the deep negative component of the P wave in lead V₁ (left atrial enlargement [LAE]). QRS voltage is markedly increased in the precordial leads, clearly exceeding the limits that define left ventricular hypertrophy (LVH). In view of the clinical profile of this patient and the history of progressive dyspnea, congestive (dilated) cardiomyopathy with

multichamber enlargement is likely. The presence of right axis deviation (RAD) in association with the clinical picture and combined ECG findings of RAE, LAE, and LVH strongly suggest that there is also enlargement of the fourth cardiac chamber (right ventricular hypertrophy [RVH]). ❖

Readers are Invited

Readers are invited to submit questions or comments on material seen in or relevant to *Internal Medicine Alert*. Send your questions to: Neill Larmore—Reader Questions, *Internal Medicine Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. For subscription information, you can reach the editors and customer service personnel for *Internal Medicine Alert* via the Internet by sending e-mail to neill.larmore@ahcpub.com. We look forward to hearing from you. ❖

In Future Issues:

Mortality Among Patients Admitted to the Hospital on Weekends Compared to Weekdays