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Norovirus Infection

ABSTRACT & COMMENTARY

Synopsis: *Noroviruses are the most common cause of gastroenteritis in the United States, accounting for approximately 23 million cases annually.*

Source: CDC. *MMWR Morb Mortal Wkly Rep*. 2003;52:41-45.

Noroviruses are a frequent cause of acute gastroenteritis. During the last 2 months of 2002 in a single health district in Washington state, 10 outbreaks of acute gastroenteritis attributable to norovirus were investigated. These events affected 354 patients in 6 long-term care facilities, a community hospital, an outpatient clinic, and the county jail.

In New Hampshire in 2002, 29 outbreaks of norovirus gastroenteritis in long-term care facilities (28 in a single month) and 2 outbreaks each in restaurants, schools, and residential summer camps were investigated. These investigations implicated person-to-person, food-borne, and water-borne transmission in 32, 2, and 1 outbreak, respectively.

Investigation of 66 outbreaks affecting approximately 1700 people in New York City occurring during 2 winter months of 2002-2003 implicated norovirus infection. Fifty-one percent occurred in nursing homes, long-term care facilities, and rehabilitation facilities; 10 in hospitals; 3 in restaurants; and 1 each in a school and a homeless shelter.

Of 27 norovirus outbreaks investigated by the CDC, 11 (41%) were caused by a single strain, the Farmington Hill strain. Although not epidemiologically related, 6 of the Farmington Hill strain outbreaks occurred on land and 5 on cruise ships.

COMMENT BY STAN DERESINSKI, MD, FACP

In 1972, viral particles were detected by immune electron microscopy in the stools of volunteers at the NIH who had ingested filtrates of stool obtained during an outbreak of diarrheal illness.[1] The virus was named after the site of that 1968 outbreak in Norwalk, Ohio.[2] Many subsequent outbreaks of what was called winter vomiting disease were found to be caused by Norwalk-like viruses, now

VOLUME 25 • NUMBER 7 • APRIL 15, 2003 • PAGES 49-56

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INSIDE

called noroviruses. This small, positive-sense, single-stranded RNA virus belongs to the family *Calciviridae*. Noroviruses have resisted cultivation, and there are no animal models. The development of an RT-PCR assay on stool has facilitated our understanding of the epidemiology of norovirus infection.

While outbreaks of norovirus infection on cruise ships have been in the news lately,[3] the majority of outbreaks occur in settings on land such as nursing homes, restaurants, schools, and day care centers. Noroviruses may also account for more than 10% of sporadic cases of gastroenteritis in both children and adults. In 1996-1997, 86 of 90 outbreaks (96%) of nonbacterial gastroenteritis in the United States were due to Norwalk-like viruses.[4] The incidence of norovirus infections appears to be increasing for reasons that are not understood.

The illness caused by Norovirus often presents, after an incubation period of 24-48 hours, with vomiting, diarrhea, nausea, and abdominal pain. Fever occurs in no more than one-half of cases and is low grade and transient. The illness generally lasts 1-3 days. The features that identify an outbreak of gastroenteritis as possibly due to Norovirus are listed in the Table.[5]

Table

Features of Gastroenteritis Outbreaks Consistent with Norovirus

Etiology

- failure to detect a bacterial or parasitic pathogen in stool specimens
- vomiting in > 50% of patients
- mean duration of illness of 12-60 hours
- mean incubation period of 24-48 hours

Cases result from ingestion of contaminated food or water or from direct person-to-person transmission. Implicated food is characteristically served cold such as salads and sandwiches. Norovirus is probably also transmitted by droplet formation from vomitus. Persistent environmental contamination may be important in the epidemiology of the disease. Environmental contamination and person-to-person transmission account for secondary cases occurring in outbreaks, a feature characteristic of norovirus disease.

The infectious dose is as few as 10 viral particles. Asymptomatic shedding may persist for up to 2 weeks, and the virus is stable in the environment, being capable of surviving freezing, heating to 60°C, and as much as 10 ppm of chlorine. These factors, together with its multiple modes of transmission, wide strain diversity, and the transient nature of immunity to infection, account for the frequent outbreaks due to norovirus.[6]

Vaccine development may be problematic, given the existence of multiple strains of norovirus, as well as the transient nature of immunity after infection. In the meantime, the only means of control is prevention by maintenance of good food, environmental, and personal hygiene. ■

Dr. Deresinski is Clinical Professor of Medicine, Stanford; Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center, Santa Clara, Calif.

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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.

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GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Internal Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $20. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $289
(Student/Resident rate: $145).

Multiple Copies
1-9 additional copies: $215 each; 10 or more copies: $191each.

Canada
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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, 2003. 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.

Statement of Financial Disclosure

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Nonsteroidal Antiinflammatory Drugs as a Risk Factor for Acute Diarrhea: A Case Crossover Study

ABSTRACT & COMMENTARY

Synopsis: *Recent NSAID use is a risk factor for acute diarrhea, a consideration for general physicians along with GI specialists.*

Source: Etienney I, et al. *Gut*. 2003;52:260-263.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDs) are widely used. It is widely appreciated that they can lead to upper gastrointestinal mucosal lesions. More recent data have verified that NSAIDs also can damage the small intestine and colon, including up to 60% demonstrable enteropathy, as well as cases of severe colitis. NSAIDs may also be related to ischemic colitis or to activation of idiopathic inflammatory bowel disease. However, there are few data describing diarrhea as a common sequela of NSAID use.

The present study was a large physician survey in France regarding patients presenting with acute diarrhea including a specific history of NSAID exposure to any of 12 different NSAIDs during several intervals prior to diarrhea onset. All of these patients were felt to have diarrhea of sufficient severity to warrant a stool study (approximately 5% of all acutediarrhea cases in general practice). Relative risk of diarrhea was dramatically increased after NSAID therapy after 1 or 3 or 6 days of exposure to NSAIDs. Intestinal pathogens were found in 16.8% of cases. Diarrhea had been present for an average of 5 days (1 to 30 days) with bleeding in 10% of patients and fever in 44% of patients.

COMMENT BY MALCOLM ROBINSON MD, FACP, FACG

It seems likely that severe NSAID colitis represents an extreme consequence of nonsteroidal drug administration. However, all physicians should be aware that NSAIDs can be a significant risk factor for acute diarrhea in general. Discontinuation of NSAID therapy may well prove to be adequate therapy for many of these patients. ■

Drug Treatments to Prevent Breast Cancer

ABSTRACT & COMMENTARY

Synopsis: *Only tamoxifen has enough evidence to be recommend for the prevention of breast cancer, and its use is limited to very high-risk women with a low risk of side effects.*

Source: Cuzick J, et al. *Lancet*. 2003;361:296-300.

EPIDEMIOLOGISTS FROM ENGLAND, ITALY, AND AUSTRALIA reviewed the combined results of breast cancer prevention trials and added updated results (*see Table*). Reports are now available on 4 trials using tamoxifen, 20 mg daily for 5 years, for prophylaxis against breast cancer. In addition, data are available on the effect of raloxifene, derived from the trial investigating raloxifene prophylaxis against fractures in women with osteoporosis.

The combined data indicated a 48% reduction in estrogen receptor-positive cancers and no effect on the incidence of estrogen receptor-negative cancers. The overall relative risk of endometrial cancer with tamoxifen was increased to 2.4, and the relative risk of venous thromboembolic events was 1.9. The length of follow-up and patient numbers do not allow data regarding breast cancer mortality. Cuzick and colleagues estimated the effect of 5 years of tamoxifen treatment, given appropriate survival rates, and concluded that 1000 high-risk women would demonstrate an 18% reduction in mortality within 10 years of diagnosis.

COMMENT BY LEON SPEROFF, MD

Cuzick et al concluded that the evidence supports tamoxifen reduction of the risk for estrogen receptor-positive breast cancer. But at the same time, they believe that tamoxifen should not be recommended as a preventive agent, except for women at very high risk. This conclusion is based upon the degree of reduction in risk compared with the incidence of side effects. The data are too limited to support the use of raloxifene as prophylactic treatment, and a stronger position awaits the outcome of the STAR trial comparing tamoxifen with raloxifene. The Medical Research Council of the United Kingdom and the National Cancer Institute of the United States have reached similar conclusions.

The evaluation by the National Cancer Institute is very helpful.[1] This report is the result of a workshop

directed to the development of a program to select the best candidates for tamoxifen treatment. Because the risks associated with tamoxifen (endometrial cancer, stroke, pulmonary embolism, and deep vein thromboembolism) increase with age, balancing the risks and benefits indicates that tamoxifen is best for younger women with an elevated risk of breast cancer (an increased relative risk of approximately 1.7). A similar conclusion was reached by a working group of the American Society of Clinical Oncology.[2] This means that only a relatively small number of women will qualify because 85% of women who develop breast cancer do not have an identifiable risk factor.

I am still concerned that the favorable conclusion regarding tamoxifen for prevention is influenced by the American results. The other 3 trials did not achieve statistical significance, results that are usually dismissed on the basis of trial size—the American trial accounted for 47% of the treated women. The recent international trial results achieved statistical significance only when ductal carcinoma in situ cases were included.[3] Nevertheless, experts and organizations in the breast cancer world have agreed that tamoxifen reduces the incidence of estrogen receptor-positive cancers in high-risk women.

Women being treated with tamoxifen for prevention of breast cancer should receive appropriate antithrombotic measures, especially during and after major surgery, and during immobility. I disagree with the National Cancer Institute's position regarding monitoring for endometrial changes, which is to simply refer the patient to a gynecologist for evaluation when the patient bleeds. Endometrial cancer is not the only side effect of tamoxifen. Women on tamoxifen treatment should be examined every 6 months to detect the emergence of endometriosis, ovarian cysts, and uterine enlargement. I believe annual measurement of endometrial thickness by transvaginal ultrasonography is indicated, recognizing that interpretation is difficult and often requires saline instillation (sonohysterography) in order to make accurate measurements. The use of the levonorgestrel-releasing IUD is highly recommended as prophylactic treatment. Interestingly, at the San Antonio Breast Cancer Symposium in December 2002, a study was presented finding no effect of postmenopausal hormone therapy against tamoxifen-induced hot flushing, when the 2 treatments were administered concomitantly. Hot flushing on tamoxifen is best treated with a serotonin uptake inhibitor.

Important questions remain unanswered. Will long-term follow-up reveal an incidence of tamoxifen-resistant cancers, cancers that are actually stimulated by tamoxifen? Will the incidence of estrogen receptor-negative cancers increase over time? What is the effect of tamoxifen treatment on quality of life and cognition (including the risk of Alzheimer's disease)? ■

Table

Trial Data

Trials	Breast Cancers	Endometrial Ca	VTE
Royal Marsden	62 vs 75	6 vs 2	12 vs 8
American	124 vs 244	36 vs 15	53 vs 28
Italian	34 vs 45	(all no uterus)	10 vs 9
International	69 vs 101	11 vs 5	43 vs 17
MORE (Raloxifene)	15 vs 43	1 vs 5	32 vs 12

Dr. Speroff is Professor of Obstetrics and Gynecology Oregon Health Sciences University, Portland, Ore.

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Diabetic Neuropathy

ABSTRACT & COMMENTARY

Synopsis: *This study shows that intravenous amantadine is beneficial in reducing the pain of painful peripheral neuropathy, with an effect sustained for at least 1 week after an infusion.*

Source: Amin P, Sturrock ND. *Diabet Med*. 2003;20:114-118.

Almost all patients with diabetes eventually develop neuropathy. New therapeutic options for the control of painful diabetic neuropathy are constantly being investigated. Many agents are effective, including anticonvulsants, tricyclic antidepressants (TCA), serotonin reuptake inhibitors, and analgesics. None work in all patients, and all have unwanted side effects. Amantadine, a noncompetitive N-methyl-D-aspartate (NMDA) antagonist, is the latest agent to show promise.

Twenty diabetic neuropathy patients were randomized into a double-blind, placebo-controlled, crossover trial of 200-mg intravenous amantadine infused once weekly for 2 weeks following an initial 28-day analgesic wash-out period and a single placebo infusion. Type 1 or

type 2 diabetics were eligible and had at least 6 months of painful diabetic neuropathy diagnosed clinically with or without abnormal electrodiagnostic studies. Exclusionary criteria included other causes of peripheral neuropathy, renal insufficiency, pregnancy, prostatism, or psychiatric history. Outcome measurements comprised a 100-mm visual analogue scale for pain intensity and pain relief, the Neuropathy Symptom Score, and Physician's Global Evaluation. Statistical analysis was provided by Student's t-test.

Seventeen patients completed the study; a foot ulcer, a transient ischemic attack, and the need for opiates excluded 1 patient each. Most were male (n = 9), type 2 diabetic (n = 15), and Caucasian (n = 16), with a mean duration of diabetes for 21 years and neuropathy for 29 months. Mean age was 58.4 years, and prior treatments included TCA (n = 6), carbamazepine, gabapentin, or paracetamol (3 each), capsaicin or nonsteroidals (2 each), and acupuncture (n = 1). Compared to placebo, amantadine infusion resulted in significant improvement in all measured ways. Intravenous amantadine provided relief from painful diabetic neuropathy, and the improvement was sustained for at least 1 week following infusion.

COMMENT BY MICHAEL RUBIN, MD

Hyperglycemia, the clear and proximate antecedent of diabetic neuropathy, sets off a plethora of metabolic abnormalities leading to oxidative stress and mitochondrial malfunction, resulting in neuronal and Schwann cell apoptosis and consequent neuropathy.[1] Metabolic abnormalities include enhanced aldose reductase activity with resultant sorbitol and fructose accumulation and myoinositol depletion in nerve. Protein kinase C is inappropriately activated, advanced glycation end products are produced, and oxygen free radicals are generated. Diabetic neuropathy is multifactorial.

Hedgehog (Hh) proteins, including sonic, desert, and indian Hh protein, are crucial for normal nervous system development—sonic Hh (SHh) protein in the central nervous system and desert Hh (DHh) protein in the peripheral nervous system. DHh is found only in Schwann cells, and in diabetic rats DHh mRNA is reduced.[2] Complete normalization of motor and sensory nerve conduction velocities was achieved with infusion of SHh-IgG (ibid.), suggesting that therapeutic benefit may accrue from this management strategy.

Overt clinical hyperglycemia may not be a prerequisite for the development of neuropathy.[3] Among 73 patients with peripheral neuropathy of unknown cause who completed an oral glucose tolerance test, 41 (56%) were abnormal. Diabetes (defined as fasting glucose > 126 mg/dL or 2-hour postglucose challenge > 200 mg/dL) was found in 15 and impaired glucose tolerance in 26 (IGT, fasting glucose 110-126 mg/dL or 2-hour postglucose challenge 140-200 mg/dL). IGT patients predominantly suffered from small fiber neuropathy, as documented by distal leg intraepidermal nerve fiber densities and had less severe large-fiber neuropathy compared to those with diabetes. Diabetes may cause significant painful neuropathy before it is evident, and all idiopathic painful polyneuropathy patients should undergo oral glucose tolerance testing. ■

Dr. Rubin is Professor of Clinical Neurology, New York Presbyterian Hospital-Cornell Campus, New York, NY.

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Pharmacology Update

Azelaic Acid Gel 15% (Finacea—Berlex)

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

AZELAIC ACID GEL HAS BEEN APPROVED FOR THE treatment of mild-to-moderate rosacea. This naturally occurring saturated dicarboxylic acid is formulated in an aqueous gel for this indication. Azelaic acid is currently available as a 20% cream (Azelex) for the treatment of acne vulgaris. The new 15% gel formulation represents the first drug approved for the treatment of rosacea in more than a decade. The 15% gel is to be marketed by Berlex for the treatment of rosacea under the trade name "Finacea."

Indications

Azelaic acid gel is indicated for topical treatment of inflammatory papules and pustules of mild-to-moderate rosacea.[1]

Dosage

A thin layer should be gently massaged into the affected area twice daily (morning and evening). The affected area should be cleaned with a very mild soap or soapless cleansing lotion and patted dry with a soft

towel before application. Patients should be advised to avoid spicy, thermally hot foods and drinks, and alcoholic drinks.[1] Patients hypersensitive to propylene glycol should not use Finacea.

Azelaic acid gel is supplied as 30 g tubes.

Potential Advantages

In a 15-week study comparing cream formulations of azelaic acid (20%) and metronidazole (0.75%) (n = 40), there was greater patient satisfaction for azelaic acid (92% vs 66%).[2] In addition, azelaic acid had a more favorable physicians rating of global improvement at 9 weeks.

Potential Disadvantages

Common side effects (20% vs 2% for vehicle) include burning, stinging, or tingling. These are generally mild. Skin irritation is generally more prominent during the first few weeks of treatment. If irritation persists or is excessive, discontinuation of therapy should be considered. Other side effects are scaling, dry skin, or xerosis (6-10%).[1]

Comments

Azelaic acid is formulated in an aqueous gel to improve drug penetration compared with the cream for the treatment of rosacea.[3] Efficacy was reported in 2 randomized vehicle-controlled studies involving 664 patients with mild-to-moderate rosacea.[1] Percent reduction of inflammatory papules and pustules at the end of 12-weeks ranged from 50% to 57.9% for azelaic gel compared to 38.2% to 39.9% for the vehicle. The ranges for investigators' global assessment were 61% to 62% and 40% to 48%, respectively. Comparative studies between gel formulations of azelaic acid and metronidazole are not currently available. The cost for azelaic acid gel is about 16% higher than of metronidazole gel, $36.60 compared to $31.40.

Clinical Implications

Rosacea is a common skin condition affecting middle-aged and older adults. It generally involves the cheeks, nose, chin, and forehead.[4] It is characterized by facial redness and acne-like lesions. The disease can progress from frequent blushing to rhinophyma and possible ocular inflammation. Early treatment is advisable to deter progression to more severe disease. Nonpharmacologic treatment includes avoidance of triggers such as sun exposure, spicy food, and alcohol. Pharmacologic treatment includes oral antibiotics (eg, tetracyclines, metronidazole) or topical metronidazole.[4,5] Azelaic gel provides another alternative. ■

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CME Questions

17. Acute diarrhea can be closely associated with use of:

a. antibiotics.
b. chemotherapy.
c. osmotic cathartics.
d. nonsteroidal anti-inflammatory drugs.
e. All of the above

18. The following statements regarding drug prevention of breast cancer are true *except*:

a. Tamoxifen and raloxifene are associated with an increased risk of endometrial cancer.
b. Drugs that have anti-estrogenic activity in the breast reduce the risk of breast cancer in high risk women.
c. A risk-benefit analysis indicates that only tamoxifen treatment is warranted, and only in a select group of women.
d. The long-term effect of drugs used to prevent breast cancer is not known.

Answers: 17 (e); 18 (a)

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Readers are invited to submit questions or comments on material seen in or relevant to *Internal Medicine Alert*. Send your questions to: Robert Kimball, *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 robert.kimball@ahcpub.com. We look forward to hearing from you. ■

Attention CME Subscribers

The answer to question 6 in the 2-15 issue is "c," not "d." We regret any confusion this might have caused. ■

By Louis Kuritzky, MD

Effect of Ibuprofen on Cardioprotective Effect of Aspirin

A substantial amount of literature supports the efficacy of aspirin (ASA) for primary and secondary prevention of cardiovascular disease. The benefits of aspirin for reduction of cardiovascular risk are generally attributed to effects on platelets, mediated by ASA-induced cyclooxygenase-1 inhibition. Earlier in vitro data have indicated that ibuprofen (IBU), but not rofecoxib or diclofenac, competes with the effects of ASA upon platelets, and might hence reduce or abolish the cardioprotective effects. Whether this is reflected clinically has not yet received sufficient scrutiny.

MacDonald and Wei studied more than 7000 persons in the United Kingdom who carried a hospital discharge diagnosis of MI, angina, stroke, PAD, or TIA, were on low-dose ASA (≤ 325 mg/d), and survived for at least 1 month post-hospital discharge. This population was further subdivided into persons who concomitantly received IBU (n = 187), diclofenac (n = 206), any other NSAID (n = 429), or no other NSAID (ie, ASA alone n = 6285). The outcomes of the study were all-cause mortality or cardiovascular mortality.

All-cause mortality in the ASA + IBU group was significantly higher than in the ASA alone group (P = 0.0011), but persons who used ASA in combination with other NSAIDs did not show an increased risk. Data on cardiovascular mortality were similar to that demonstrated for all-cause mortality.

MacDonald and Wei conclude that these data support the possibility that the combination of IBU with ASA may be deleterious toward cardiovascular and total mortality risk, when compared with persons taking ASA alone. The NSAID comparators, other than IBU, did not display a similar detraction to the cardiovascular benefits of ASA. ■

MacDonald TM, Wei L. Lancet. 2003; 361:573-574.

Relapse Prevention with Antidepressant Drug Treatment in Depressive Disorders

Pharmacotherapy for depression is generally recognized to be effective to produce remission in the majority of sufferers. The recommended duration of treatment of depression has undergone evolution, subsequent to the observation that brief treatments (4-6 months, or less), subject the patient to increased risk of relapse and recurrence.

Geddes and colleagues studied the efficacy of antidepressant treatment to prevent recurrence when continued into long-term (ie, > 6 months) treatment. Pooling data from 31 randomized trials (n = 4410), they evaluated the likelihood of relapse when a patient continued whatever pharmacotherapy had effected a remission, compared with the relapse rate for persons on placebo. The antidepressants included in the meta-analysis include tricyclics, SSRIs, and heterocyclic agents.

The results were consistent across all antidepressants evaluated: continuing therapy reduced the risk of relapse by approximately one half. Only 6 trials reported very long-term data (> 2 years), but even in this patient population, continued antidepressant therapy reduced risk of relapse by more than 50%.

Geddes et al conclude that in persons who respond to antidepressant therapy, continuation of medication produces substantial reduction in likelihood of relapse, which does not appear to diminish even in long-term maintenance trials. ■

Geddes JR, et al. Lancet. 2003;361: 653-661.

Incidence and Preventability of Adverse Drug Events Among Older Persons in the Ambulatory Setting

When one considers that more than 90% of persons older than age 65 use at least 1 medication per week, and that more than 40% of these individuals use 5 or more medications per week, it should come as no surprise that adverse events, even in the ambulatory setting, may occur. Although more attention has been given recently to hospital and nursing home medication misadventures, less scrutiny of ambulatory adverse events, and their potential for prevention, is available.

The population studied (n = 27,617) comprised predominantly persons enrolled in a Medicare + Choice Plan. Adverse events were tabulated for a 12-month period. When adverse events related to medications were identified (n = 1523), a physician panel adjudicated whether the event was preventable.

Cardiovascular drugs were the class most often represented by adverse effects (26%), followed by antimicrobials (14.7%), diuretics (13.3%), nonopioid analgesics (11.8%), and anticoagulants (7.9%). More than one fourth of the adverse medication related events were judged preventable by the clinician review. Among the serious, life threatening, or fatal adverse events, a substantially greater portion was judged to be preventable: 42.4%.

Medication-related adverse events are commonplace and not infrequently serious. Since a substantial number of such events are judged to be preventable, enhanced strategies for risk reduction are needed. ■

Gurwitz JH, et al. JAMA. 2003;289:1107-1116.

What Might the Echo Show?

By Ken Grauer, MD

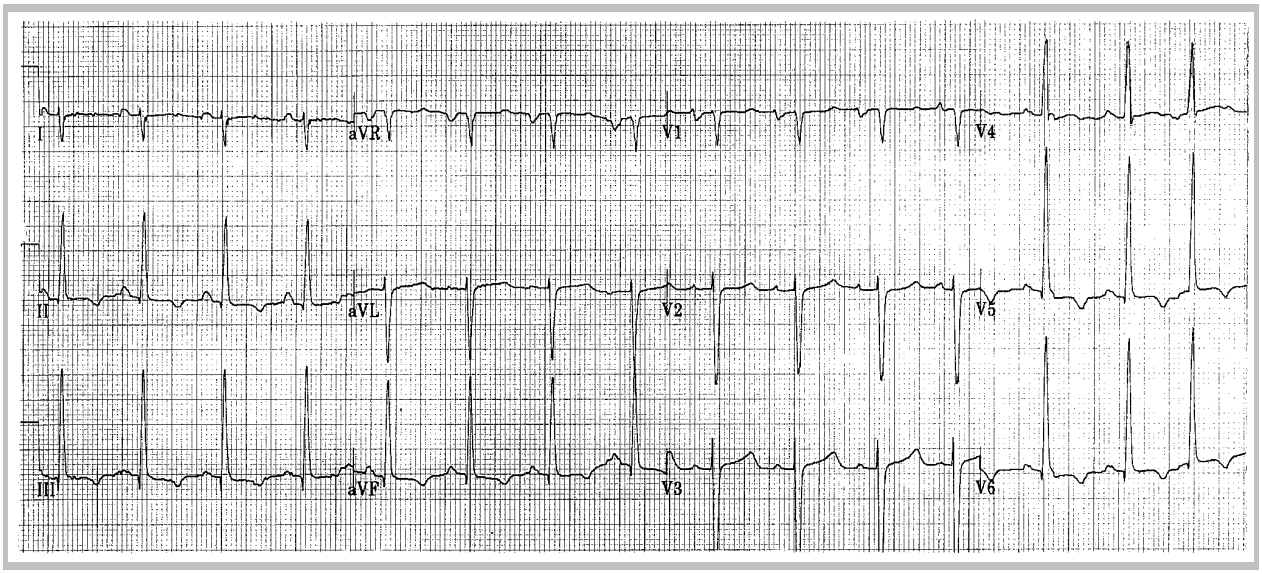

Figure. ECG obtained from a 55-year-old man with heart failure and emphysema.

Clinical Scenario: The ECG in the Figure was obtained from a 55-year-old man with a history of heart failure and emphysema. What might his echocardiogram show?

Interpretation: The rhythm is sinus at a rate of about 90 beats/minute. Occasional PACs (premature atrial contractions) are seen (4th beat in lead V_1; 3rd beat in lead V_4). There is a marked RAD (right axis deviation). Assessment for hypertrophy suggests four chamber enlargement. Small q waves are present in the inferior and lateral precordial leads. ST-T wave abnormalities in these same leads is consistent with "strain," although the slight ST segment coving in leads V_5, V_6 in association with fairly symmetric T wave inversion could also reflect ongoing ischemia.

In general, the ECG is an insensitive indicator of chamber enlargement. When assessment of chamber enlargement and function is essential to patient management, echocardiography should be obtained. That said, interpretation of the ECG pattern in the context of the clinical setting can suggest the anatomic substrate in selected cases. The patient in this case was known to have pulmonary disease (emphysema) and heart failure. The ECG in the Figure is diagnostic of LVH (left ventricular hypertrophy), in that there is a deep S wave in lead V_2, and very tall R waves in leads V_5 and V_6 that occur in association with ST-T wave changes of "strain." Although the pattern of RAD seen here is consistent with LPHB (left posterior hemiblock), this type of hemiblock rarely occurs as an isolated conduction defect. Therefore, the RAD seen in this tracing is much more likely to reflect RVH (right ventricular hypertrophy). The deep negative component to the P wave in lead V_1 suggest that RAE (right atrial enlargement) may also be present, although admittedly these P waves are not quite as tall as desired to fully satisfy ECG diagnostic criteria. ■

In Future Issues: Warfarin and VTE

PHARMACOLOGY WATCH

Warfarin Effectively Prevents Venous Thromboembolism

Low intensity warfarin therapy effectively prevents recurrent venous thromboembolism, according to a recent study in the *New England Journal of Medicine*. After a median of 6.5 months of full-dose anticoagulation therapy, 508 patients with idiopathic venous thromboembolism were randomized to placebo or low intensity warfarin therapy with target INRs of 1.5 to 2.0. The study was terminated early after 4.3 years of follow-up due to a marked reduction in recurrent thromboembolism in the low intensity warfarin therapy group. Of 253 patients assigned to placebo, 37 had recurrent venous thromboembolism compared with 14 of 255 patients assigned to low intensity warfarin, a risk reduction of 64% (hazard ratio 0.36; [95% CI, 0.19-0.67]; $P < 0.001$). Major hemorrhage occurred in 2 patients assigned to placebo and in 5 assigned to low intensity warfarin ($P = 0.25$). Death occurred in 8 patients in the placebo group and 4 in the low intensity warfarin group ($P = 0.26$). The composite end point was recurrent venous thromboembolism, major hemorrhage, or death. There was a 48% reduction in the composite end point with low intensity warfarin therapy. Because of the importance of these findings, the journal published the study online more than a month prior to its publication date of April 10, 2003.

Vitamin D Reduces Osteoporotic Fractures

British researchers have reduced the rate of osteoporotic fractures in older adults by mailing low-cost vitamin D3 supplements to study subjects every 4 months. Researchers from Cambridge and Oxford universities randomized 2686 adults age 65-85 (2037 men and 649 women) to 100,000 IU vitamin D3 or placebo every 4 months for 5 years. The active medication and placebo were sent to patients by mail and compliance was tracked by completion of a form. At the end of the study period, 149 fractures were noted in the control group and 119 were noted in the vitamin D3 group (RR = 0.78). Fractures of the hip, wrist, forearm, or spine were considered osteoporotic fractures, of which 87 were noted in the control group and 60 in the vitamin D3 group (RR = 0.67). The vitamin D treatment was well tolerated and cost less than 1 pound per year. The authors suggest that vitamin D may be a good, inexpensive primary prevention strategy for the prevention of osteoporotic fractures (*BMJ*. 2003;326:469-472).

Adefovir Effective for Hepatitis B Treatment

Adefovir is an effective treatment for chronic hepatitis B, according to 2 studies published in February. The first study from Greece randomly assigned 185 patients (in a 2:1 fashion) with e antigen-negative chronic hepatitis B, to 10 mg of adefovir or placebo daily for 48 weeks. Patients in the adefovir group were significantly more likely to have improvement in histologic abnormalities as shown by liver biopsy compared to placebo (64% improvement [77 of 121] adefovir group, 33% [19 of 57] placebo group; $P < 0.001$). Patients in the treatment group also had reduced hepatitis B virus DNA levels and improved alanine aminotransferase levels compared to placebo. Resistant hepatitis B virus was not noted, and the drug was well tolerated (*N Engl J Med*. 2003;348:800-807). In a second multinational study of

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e antigen-positive chronic hepatitis B, 515 patients were randomized to adefovir 10 mg/d, adefovir 30 mg/d, or placebo for 48 weeks. The primary end point was histologic improvement, which was noted in 53% of the 10 mg group, 59% of the 30 mg group, and 25% of the placebo group ($P < 0.001$ for both dose schedules). Once again, evidence of hepatitis B virus was markedly reduced, and there was significant normalization of alanine aminotransferase levels in both treatment groups. The safety profile of 10 mg/d adefovir was similar to placebo; however, there was a higher frequency of adverse events and renal laboratory abnormalities in the 30 mg/d group. Again no hepatitis B virus mutations were noted in the treatment groups. The authors conclude that 10 mg/d adefovir is a favorable risk benefit profile for long-term treatment of e antigen-positive chronic hepatitis B (*N Engl J Med*. 2003;348:808-816). An accompanying editorial states "we appear to be at the dawn of the new era" in the treatment of hepatitis B (*N Engl J Med*. 2003;348:848-850).

Ibuprofen/Aspirin Study Revisited

Another study suggests that ibuprofen blocks the cardioprotective effects of aspirin. In 2001, researchers showed that ibuprofen may block the COX-1 receptor on platelets, keeping aspirin from binding to the receptor (*N Engl J Med*. 2001;345:1807-1817). Now a new study suggests that ibuprofen may reduce the cardioprotective effect of aspirin. Researchers in the United Kingdom reviewed the records of more than 7000 patients who were admitted for MI, angina, stroke, TIA, or peripheral vascular disease and were given aspirin at discharge.

All survived at least 1 month post discharge. In addition to aspirin, 187 patients were also prescribed ibuprofen and 206 were prescribed diclofenac. The patients who took the aspirin/ibuprofen combination were associated with significantly higher all-cause mortality (hazard ratio, 1.93 [$P = 0.011$]) and higher cardiovascular mortality (hazard ratio, 1.73 [$P = 0.0305$]) compared to patients who took aspirin alone. There was no adverse effect noted with aspirin/diclofenac (*Lancet*. 2003;361:573-574). An accompanying editorial suggests that the lack of effect of diclofenac may be due to its relative COX-2 selectivity. The author also suggests that because of the wide availability of over-the-counter ibuprofen, physicians need to be vigilant and explain this potential drug-drug interaction to patients on aspirin cardioprotection (*Lancet*. 2003;361:542-544).

ACE Inhibitors Favored in Cardiovascular Care

A head-to-head study of ACE inhibitors vs diuretics for the treatment of hypertension suggests that ACE inhibitors are better at reducing cardiovascular events. The Second Australian National Blood Pressure Study (ANBP2) compared ACE inhibitors to diuretics and a perspective, randomized, open-label study with blinded assessment of end points. More than 6000 hypertensive men and women age 65-84 were followed for a median of 4.1 years. The drug treatment was titrated to a similar level of blood pressure lowering (a decrease of 26/12 mm Hg). The end point was the total number of cardiovascular events in the 2 treatment groups. There were 695 events in the ACE inhibitor group (56.1/1000 patient years) and 736 events in the diuretic group (59.8/1000 patient years). The hazard ratio for the ACE inhibitor group was 0.89 (95% CI, 0.79-1.00 [P = 0.05]). The hazard ratio for male patients was 0.83 and for female patients was 1.00. The authors conclude that treatment of hypertension with ACE inhibitors leads to better cardiovascular outcomes than treatment with diuretics, particularly in older men (*N Engl J Med*. 2003;348:583-592). The results of this study seem to contradict the recently published ALLHAT study which showed better outcomes with diuretics (*JAMA*. 2002;288:2981-2997).

Digoxin Dosing and Heart Failure

If digoxin is to be used in men with heart failure, serum digoxin concentrations (SDC) are optimal between 0.5 to 0.8 ng/dL, according to further analysis of the Digitalis Investigation Group (DIG) trial. The initial reports of DIG reported that digoxin provided no overall mortality benefit and only modest reduction in hospitalizations among patients with heart failure and depressed left ventricular function. This new study looked at outcomes in 1171 men based on SDC of 0.5-0.8 ng/mL, 0.9-1.1 ng/mL, and greater than or equal to 1.2 ng/mL, compared to 2611 men randomly assigned to receive placebo. The main outcome was all-cause mortality of follow-up of 37 months. The highest SDC were associated with higher all-cause mortality. Patients in the lowest SDC range(0.5-0.8ng/mL) had a 6.3% lower mortality rate compared with patients receiving placebo (95% CI, 2.1-10.5). Patients in the midrange SDC (0.9-1.1 ng/mL) had no reduction mortality, while patients with the SDCs above 1.2 ng/mL had 11.8% higher mortality rate than those receiving placebo (95% CI, 5.7-18%). The authors conclude that higher serum digoxin concentrations were associated with increased mortality and that the optimal SDC for men with heart failure is 0.5-0.8 ng/mL, and the authors suggest this for the new optimal therapeutic range (*JAMA*. 2003;289:871-878). ■