AMERICAN HEALTH CONSULTANTS®

INTERNAL MEDICINE ALERT®

Providing Evidence-based Clinical Information for 24 Years

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

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

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

Got Milk?

ABSTRACT & COMMENTARY

Synopsis: *Dairy food intake is inversely associated with the risk of the insulin resistance syndrome.*

Source: Pereira MA, et al. *JAMA.* 2002;287:2081-2089.

This paper is a product of the ongoing Coronary Artery Risk Development in Young Adults (CARDIA) Study, a prospective evaluation of more than 5000 people aged 18-30 years.[1] At intake and at 7 years, questionnaires were used to collect information on diet, activity, cigarette smoking, demographics, and education. Pereira and colleagues included laborious detail on collection and assessment of dietary information. Milk, milk drinks, butter, cream, and cheeses made up about 90% of dairy intake in this sample. They also collected data on and control for other dietary factors such as whole grains, soft drinks, fish, and fruits. Physical measurements included height, weight, body mass index (BMI), waist to hip ration (WHR), and blood pressure. Laboratory data included fasting triglycerides, insulin, glucose, and HDL-C measurements. A total of 3157 participants were included in this analysis.

The insulin resistance syndrome (IRS) was defined as 2 or more of the following 4 components:

1. abnormal glucose homeostasis (fasting plasma insulin concentration of at least 20 micro units per milliliter, fasting glucose concentration of at least 110 mg/dL, or the use of medications to control blood glucose);
2. obesity (BMI of at least 30 kg/m^2 or a WHR of at least 0.85 for women or 0.90 for men);
3. elevated blood pressure (at least 130/85 or the use of antihypertensives); or
4. dyslipidemia (HDL-C < 35 mg/dL or triglyceride > 200 mg/dL).

Dairy intake was higher in whites than in blacks, and lower in overweight individuals than in normal-weight individuals. Dairy consumption was positively associated with whole grain, fruit, vegetable, and saturated fat intake, and negatively associated with sugar-sweetened soft drink intake.

Incidence rates for IRS were higher for individuals who were

VOLUME 24 • NUMBER 10 • MAY 29, 2002 • PAGES 73-80

INSIDE

Gastroenteritis-associated hyperamylasemia **page 75**

Cardiovascular dangers of ma huang **page 75**

Which androgen for the andropause? **page 76**

H pylori and dyspepsia **page 77**

Pharmacology Update: *Pegfilgrastim* **page 78**

overweight (BMI > 25 kg/m^2) at baseline and for blacks. For overweight individuals, there was a consistent reduction in the incidence of each of the 4 components of the IRS with increasing intake of dairy products; there was a much weaker relationship between dairy intake and these findings in normal weight individuals. For overweight individuals, the odds ratio (OR) for IRS was strongly and inversely correlated with dairy intake, with an OR of 0.29 for those in the highest dairy intake category (35 or more servings per week), and 1.15 for those in the lowest dairy intake category (0-10 servings per week). This relationship was essentially unchanged by controlling for demographics, nondietary lifestyle factors, dietary fiber, and protein. This relationship seemed independent of whether the diary intake was high fat or low fat. Fiber and diary intake appeared to have a joint independent effect on reduction of IRS. Increasing dietary protein appeared to increase the incidence of IRS. In general, the odds of IRS were lowered about 21% for each daily eating of dairy products.

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

When was the last time you had an overweight patient who walked in drinking milk? While this hardly ever happens, the number of obese individuals who blithely walk into my office carrying caffeinated, carbonated, sugar-filled, calorie-filled beverages in soda pop cans is astonishing.

Some prior evidence suggests that dairy products could have beneficial effects on weight control.[2,3] It is possible that the lactose, fat, and protein in dairy products could affect satiety and perhaps reduce intake of calories in other forms (for example, soft drinks). Another possibility is that calcium or magnesium in dairy products could account for the findings presented here. Calcium and/or dairy intake may be associated with a decreased risk of cardiovascular disease.[4-6] In the current study, however, Pereira et al found no meaningful change in the results when they controlled for intake of high carbohydrate foods or calcium.

The IRS, also known as the metabolic syndrome or syndrome X, is a constellation of risk factors that increases the risk of cardiovascular disease and diabetes. Its prevalence appears to be increasing, and this may account in part for the plateau of previously-declining cardiovascular disease rates.

It is notable that the increasing prevalence of IRS coincides with the increasing amount of soda ingestion by adolescents and young adults, while dairy product consumption (chiefly milk) has declined.[7] Pereira et al conclude that ". . .increased dairy consumption may protect overweight individuals from the development of obesity and the IRS, which are key risk factors for type 2 diabetes and cardiovascular disease." My belief is that their recommendation, while supported by this study, will only work if individuals replace some intake (preferably soft drinks) with milk, rather than simply increasing total intake by adding milk on. With obesity, the basic problem remains one of taking in more calories than are being burned. ■

References

1. Friedman GD, et al. *J Clin Epidemiol.* 1988;41: 1105-1116.
2. Carruth BR, Skinner J. *Int J Obes Relat Metab Disord.* 2001;25:5559-5566.
3. Zemel M, et al. *FASEB J.* 2000;14:1132-1138.
4. Ascherio A, et al. *Hypertension.* 1996;27:1065-1072.
5. Bostick RM, et al. *Am J Epidemiol.* 1999;149:151-161.

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.

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.

THOMSON™
AMERICAN HEALTH CONSULTANTS

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, 2002. 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 consultant for Aventis. 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, Merck, Res Med, and GlaxoSmithKline and is a consultant for Boehringer Ingelheim, Wyeth-Ayerst, and Res Med. Dr. Robinson serves as a consultant for TAP, Pfizer, Janssen, Eisai, J&J-Merck, and Procter & Gamble, is on the speaker's bureau of Janssen, Eli Lilly, Solvay, TAP, and Aventis, and does research for Forest Labs, Wyeth-Ayerst, AstraZeneca,and Centocor. Drs. Chan, Elliott, Ferris, Grauer, Karpman, Wiese, and Wilke report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

6. Abbott RD, et al. *Stroke.* 1996;27:813-818.
7. Cavadini C, Siega-Riz Am, Popkin BM. *Arch Dis Child.* 2000;83:18-24.

Gastroenteritis-Associated Hyperamylasemia: Prevalence and Clinical Significance

ABSTRACT & COMMENTARY

Synopsis: *Mild-to-moderate elevations of serum amylase can be associated with nonspecific gastroenteritis.*

Source: Ben-Horin S, et al. *Arch Intern Med.* 2002;162: 689-692.

Clinicians have come to depend on serum amylase elevations as a useful index for inflammation of the pancreas. It is known that "spurious" amylase elevations can occur in certain other conditions such as salivary gland disease, intestinal perforation, and renal failure. Although gastroenteritis is not widely appreciated as a cause of amylase elevation, there have been a few reports that suggest this association. Ben-Horin and colleagues describe findings from 1041 patients with a diagnosis of acute gastroenteritis in a hospital emergency department. Amylase values were available for 67% of patients, and 9.4% were found to have elevated amylase values up to 2.2 times normal. Of these patients, many had normal prior amylase levels before their hospital referral for gastroenteritis; others had normal follow-up amylase results within a month after these acute episodes. The amylase values did not correlate with clinical course, nor was there any relation to age or sex or other laboratory parameters. It was speculated that hyperamylasemia could be due to pancreatic inflammation occurring as part of the infectious inflammatory gastroenteritis process. Alternatively, and perhaps more likely, increased mucosal permeability during gastroenteritis could allow backflow of pancreatic enzymes from the gut lumen to the bloodstream.

COMMENT BY MALCOLM ROBINSON MD, FACP, FACG

This study is of interest to clinicians and provides a useful perspective on the possible association of elevated amylase values and acute gastroenteritis—in the absence of clinically relevant pancreatic disease. These observations are limited by their retrospective nature, but it seems likely that they would be confirmed by a suitable prospective study. In patients with apparent gastroenteritis and amylase values up to twice normal, it would be reasonable to assume that such enzyme elevations are nonspecific and that they need not mandate further pancreatic evaluation or any unusual therapeutic intervention. ■

Cardiovascular Dangers of Ma Huang

ABSTRACT & COMMENTARY

Synopsis: *This study concluded that ma huang use was temporally related to stroke, MI, and sudden death.*

Source: Samenuk D, et al. *Mayo Clin Proc.* 2002;77:12-16.

Many forms of alternative medical therapy are currently available but there is little question that the herbal medicines contained in weight loss products are the most commonly purchased nutritional supplements with sales estimated at $3.6 billion in 1997.[1] Ma huang is derived from the genus *Ephedra* and is a popular herb that is used in many nontraditional medications. Because it is a natural source of ephedrine, ma huang is commonly used for appetite suppression and energy enhancement.

Samenuk and associates from the Cardiac Arrhythmia Service of the New England Medical Center in Boston, Mass, evaluated the possible cardiovascular toxic effects associated with the use of dietary supplements containing ma huang. They reviewed the comprehensive Adverse Reactive Monitoring System database of the Food and Drug Administration that included the clinical records and the investigative and autopsy reports of patients who had used ma huang. The main outcome measures evaluated the occurrence of stroke, myocardial infarction (MI), and/or sudden death. They found that ma huang was temporally related to stroke in 16 patients, MI in 10, and sudden death in 11 of the 37 patients in the database. Autopsies performed on 7 of the 11 patients who died suddenly demonstrated a normal heart in 1, coronary atherosclerosis in 3, and cardiomyopathies in 3 other patients. In 36 of the 37 patients, the use of ma huang was reported to be within the manufacturers' dosing guidelines. Samenuk et al concluded that ma huang use was temporally related to stroke, MI, and sudden death, that underlying cardiovascular disease was not a prerequisite for ma huang-related adverse

events, and that the cardiovascular toxic effects associated with ma huang use were not limited to large or massive doses of the herb.

COMMENT BY HAROLD L. KARPMAN, MD, FACC, FACP

Although rigorous standards of safety and efficacy of drugs usually have to be met through appropriately designed clinical trials before a drug is made available to the public, herbal remedies and dietary supplements are protected by the "Dietary Supplements Health and Education Act of 1994" and can be withdrawn from the market only if they are proven to be "unsafe," that is, if the marketed dietary supplement has been demonstrated to present a serious or unreasonable risk under the conditions of use recommended on the label or as commonly consumed.[2] Because ma huang comes from a natural source of ephedrine, it is commonly found in weight loss and energy enhancement products. The common misconception that the substance has no associated serious medical consequences has contributed to the widespread use of the herb in many weight reduction products despite the fact that the potential cardiovascular toxic effects of ma huang had never previously been systemically evaluated.

Careful analysis of the medical records of 37 patients in the FDA Adverse Reaction Monitoring System database clearly demonstrated that the use of ma huang may be associated with serious cardiovascular and, possibly, other medical complications. It should be noted that a substantial portion of the patients studied were young, had no other risk factors for cardiovascular disease such as diabetes, hypertension, smoking, or family history of premature cardiovascular diseases, and their findings confirmed observations from other reports[3-6] that ma huang may precipitate life-threatening events. This report is limited because it is an observational study and as such does not definitively establish the relationship between ma huang use and the risk of the reported adverse cardiovascular events. In addition, even though it provided no insight into the biological mechanisms believed the possible adverse effects of ma huang or the anorectic agents in which it is used, the reported observations should raise important public health issues that warrant further research.

The incidence of complications among the 12 million people in the United States who have consumed products containing ma huang in 1999 appeared to be extremely small, however, it should be recognized that the adverse effects of these drugs are usually under reported and, more important, the agent itself has never proven scientifically to be of benefit in weight reduction regimens. However, at this time, it would seem incumbent on any physician to advise his patients not to ingest herbal remedies or other forms of alternative medications which might contain ma huang and/or more concentrated ephedrine compounds because it has now been clearly suggested that ma huang usage may be associated with a higher incidence of sudden death, MI, and stroke even in the absence of structural heart disease. ■

References

1. Canedy C. Real medicine or medicine show? Growth of herbal remedy sales raises issues about value. *New York Times.* July 23, 1998:DI.
2. Shifman NR, et al. *N Engl J Med.* 1998;339:806-811.
3. Haller CA, Benowitz NL. *N Engl J Med.* 2000;343: 1833-1838.
4. Zahn KA, Li RL, Purssell RA. *J Emerg Med.* 1999; 17:289-291.
5. Zaacks SM, et al. *J Toxicol Clin Toxiol.* 1999;37: 485-489.
6. Theoharides TC. *J Clin Pyschopharmacol.* 1997;17: 437-439.

Which Androgen for the Andropause—DHT or Testosterone?

ABSTRACTS & COMMENTARY

Synopsis: *Transdermal DHT improves sexual function and may be a useful alternative for androgen replacement.*

Sources: Kunelius P, et al. *J Clin Endocrinol Metab.* 2002; 87:1467-1472; Wang C, Swerdloff R. *J Clin Endocrinol Metab*. 2002;87:1462-1466.

Bioavailable testosterone (T) declines approximately 1% per year in men between 40 and 70 years of age. Kunelius and colleagues note that "in contrast to menopausal symptoms in women the age-related changes in testicular function in men are gradual and may be difficult to recognize. However, a number of changes typically experienced by ageing males have been attributed to a decline in circulating T levels." Diminished virility, fertility, energy, and depression as well as a decrease in bone and muscle mass and an increase in adiposity have been attributed to the decrease in T.

The objective of the study was to investigate the effects of DHT gel on general well-being, sexual func-

tion, and the prostate in aging men. A total of 120 men participated in a randomized, placebo-controlled study (60 DHT and 60 placebo). All subjects had serum T levels of 15 nmol/L or less (normal range, 10-35 nmol/L), and/or sex hormone binding globulin (SHBG) greater than 30 nmol/L. The mean age was 58 years (range, 58-70). A total of 114 men completed the study. DHT was administered transdermally for 6 months, and the doses varied between 125-250 mg/d.

Early morning erections improved in the DHT group at 3 months ($P = 0.003$) and the ability to maintain erections improved in the DHT group compared with the placebo group ($P = 0.04$). No significant changes were observed in well-being between the DHT and the placebo group (significant placebo effects were noted in the area of well-being). Serum concentrations of LH, FSH, estrogen (E2), T, and SHBG decreased significantly during the DHT treatment. Treatment with DHT did not effect liver function or the lipid profile. The hemoglobin and hematocrit both increased significantly. Prostate weight and prostate specific antigen did not change during treatment.

Kunelius et al concluded that transdermal administration of DHT improves sexual function and may be a useful alternative for androgen replacement. As estrogens are thought to play a role in the pathogenesis of prostate hyperplasia, DHT may be beneficial, compared with aromatizing androgens in the treatment of aging men.

COMMENT BY RALPH R. HALL, MD, FACP

This interesting study is complicated by several factors. First, this is a small number of patients treated for a short period of time. Second, the level of T in this group was relatively high. The normal range of T in men is 10-35 nmol/L. Using the range of up to 15 nmol/L, this study may have decreased the apparent effectiveness of the DHT treatment.

In the accompanying editorial, Wang and Swerdloff note that the decrease in E2 that occurs in nonaromatizing androgens may have several potentially negative effects. Estrogens are thought to have beneficial effects on bone mineral density, dementia, and possibly cardiovascular disease. Studies documenting bone mineral markers during DHT treatment have not been done. The lack of adverse effects of DHT in this study is encouraging but better outcome measures are needed.

There were no changes in prostate size or increases in PSA determinations to indicate unfavorable effects on the prostate. Again, E2 is thought to contribute to increases in prostate hyperplasia and at least one study has reported decreases in prostate size during treatment with DHA.[1]

Studies are needed that compare T with DHT and placebo. In order to measure the effects of T and DHT on muscle strength, groups who are sedentary need to be compared with those in a structured exercise program. These early reports on both T and DHT certainly justify longer and more comprehensive trials of both T and DHT.

There are now extensive data supporting the safety of transdermal T in men with andropause and other forms of hypogonadism. There is not enough evidence supporting the safety of long-term DHT treatment to justify its use. Before starting T, however, rectal prostate examination should be carried out and if nodules are found, prostatic biopsy carried out.

The 4-page editorial by Wang and Swerdloff, (they have vast clinical and investigative experience in this area), is a brief, up-to-date, but comprehensive review of the present status of androgen replacement in older men. ■

Reference

1. de Lignieres B. *Ann Med.* 1993;25:235-241.

H pylori and Dyspepsia: Physicians' Attitudes, Clinical Practice, and Prescribing Habits

ABSTRACT & COMMENTARY

Synopsis: *H pylori eradication is frequently and inappropriately used in uninvestigated dyspepsia.*

Source: O'Connor HJ. *Aliment Pharmacol Ther.* 2002;16(3):487-496.

Despite the wide dissemination of information regarding the pathogenetic role of *H pylori* in peptic ulcer, actual management of ulcer disease continues to involve both neglect as well as use of ineffective eradication regimens. Although there are few data to support such behavior, physicians are extremely aggressive in eradicating *H pylori* in GERD patients and in those with dyspepsia.

Many have said that the discovery of *H pylori* infection was one of the most important medical advances of the 20th century, followed by the observation that eradication of *H pylori* could effectively cure ulcer disease. This article reviews the biomedical literature available to December 2000. Many physician surveys confirmed that

both primary care physicians and gastroenterologists understood the *H pylori* ulcer relationship. Nevertheless, by 1998, less than half of US family physicians and only 64% of Italian primary care doctors routinely used *H pylori* eradication therapy for duodenal ulcer. Despite far less belief in the relationship of gastric ulcer and *H pylori*, most physicians (including gastroenterologists) used eradication therapy similarly in these disparate illnesses. Although less than 10% of physicians believed that *H pylori* had any causative role in dyspepsia, as many as two thirds of international physicians reported use of *H pylori* eradication in uninvestigated dyspeptic patients. Although European doctors were less likely to treat GERD patients for *H pylori* than surveyed American physicians, use of *H pylori* eradication in this inappropriate setting remained common on both sides of the Atlantic. Great variations were described in the choice of treatment regimens for *H pylori* eradication. One study discovered 66 different eradication regimens, and only 52% of these were deemed to be potentially efficacious. In an interesting large survey in the United Kingdom, patients who received an *H pylori* eradication regimen were documented to have subsequently received antisecretory therapy in 53% of cases in the subsequent year. Other studies elsewhere have led to similar findings.

■ **COMMENT BY MALCOLM ROBINSON MD, FACP, FACG**

It seems clear that the wide dissemination of information regarding *H pylori* and the development of many national guidelines for its management, physicians seem confused regarding appropriate care for patients with gastrointestinal disorders coupled with *H pylori* infection. Far more aggressive educational efforts must be undertaken to rectify these international misperceptions and resulting therapeutic misadventures. ■

Pharmacology Update

Pegfilgrastim (Neulasta™)—A Pegylated Form of Filgrastim

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

THE FDA HAS APPROVED A PEGYLATED FORM OF FILgrastim (Neupogen). Filgrastim is a recombinant granulocyte colony-stimulating factor (CSF) that stimulates the production and maturation of neutrophils and enhances the function of mature neutrophils. Pegylation (combining a drug with PolyEthylene Glycol) is a novel approach to modifying a parenteral drug's pharmacokinetics and, in turn, its pharmacodynamics.[1] In this case, combining filgrastim with monomethoxypolyethylene glycol permits one dose per chemotherapy cycle compared to daily dosing with filgrastim. It will be marketed by Amgen as Neulasta.

Indications

Pegfilgrastim is indicated to decrease the incidence of infection (ie, febrile neutropenia) in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapeutic agents with significant potential for febrile neutropenia.[2] Pegfilgrastim has not been studied in patients administered drugs with delayed myelosuppression (eg, nitrosoureas, mitomycin C). It should be used with caution in patients with sickle cell disease as it may precipitate a severe sickle cell crisis. Pegfilgrastim should not be used for peripheral blood progenitor cells (PBPC) mobilization as rare cases of splenic rupture have been reported with filgrastim.[2]

Dosage

Pegfilgrastim is administered as a single subcutaneous injection of 6 mg per chemotherapy cycle. It should not be given 14 days before and 24 hours after chemotherapy.[2] The recommended injection sites are outer areas of the upper arms, front of the middle thighs, upper outer areas of the buttocks, and the abdomen (except for the 2-inch area around the navel).

Pegfilgrastim is available as a 6-mg single-dose syringe.

Potential Advantages

Pegfilgrastim is administered once per chemotherapy cycle compared to daily injections for filgrastim. This amounts to 1 injection of pegfilgrastim compared to 11 injections of filgrastim. The clearance of pegfilgrastim is directly related to the number of neutrophils as clearance increases (concentration decreases) with neutrophil recovery.[2]

Potential Disadvantages

Medullary bone pain is the most common side effect and has been reported in 26% of patients. The incidence appears to be comparable to that of filgrastim.[3,4] Nonaspirin analgesics such as acetaminophen are recommended to relieve bone pain. Other side effects include redness, swelling, or itching at the injection site. Adult respiratory distress syndrome (ARDS) has been reported

in patients with sepsis who received filgrastim. Therefore, pegfilgrastim should be discontinued or withheld if ARDS occurs.[2] Pegfilgrastim is administered as a single-dose per cycle and does not permit titration to desired absolute neutrophil counts (ANC). Lithium may potentiate the release of neutrophils. There is a theoretical possibility that pegfilgrastim may stimulate the growth of certain tumors.[2]

Comments

Pegfilgrastim and filgrastim were compared in 2 multicenter, randomized, double-blind, active-control studies in patients with metastatic breast cancer who received 4 cycles of doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2. A weight-based dose of a single injection of pegfilgrastim (100 µg/kg every 21 days; n = 310) and a fixed-dose of 6 mg (n = 157) were compared to daily doses of filgrastim (5 µg/kg/d).[2,3] There was no difference in the primary end point of mean days of severe neutropenia. (1.7-1.8 days for pegfilgrastim and 1.6 days for filgrastim). In the weight-based dose study, the mean duration of severe neutropenia for cycles 2, 3, and 4 favor pegfilgrastim over filgrastim. They were 0.7, 0.6, and 0.9 days for pegfilgrastim and 1.1, 1.2, and 1.3 days, respectively, for filgrastim. Differences for cycles 2 and 3 were statistically significant at $P < 0.05$ level. A lower overall rate of febrile neutropenia was also reported (9% vs 18%; $P = 0.029$).[3] Pegfilgrastim may also be less likely to cause overshoot of neutrophils. There were no differences in adverse events such as bone pain and elevated laboratory values, although the frequency of elevated LDH (19% vs 29%) and alkaline phosphatase (9% vs 16%) were numerically lower with pegfilgrastim.[2]

Pegfilgrastim costs about $2400 per injection compared to $1700 for 11 doses of filgrastim.

Clinical Implications

Neutropenia is the most serious side effect of myelosuppressive chemotherapy in cancer patients, potentially leading to increased risk of infections and may delay the time until next doses of chemotherapy. A recent meta-analysis concluded that prophylaxis with recombinant granulocyte CSFs have been associated with a reduced risk of febrile neutropenia (odds ratio [OR] 0.38; 95% CI, 0.29-0.49; $P = 0.001$), documented infection (OR 0.51; 95% CI, 0.36-0.73; $P = 0.001$), and a trend toward reduced infection-related mortality (OR 0.60; 95% CI, 0.30-1.22; $P = 0.16$). Patients who received CSF were also less likely to have a dose reduction or treatment delay (OR 0.32; 95% CI, 0.21-0.47; $P = 0.001$).[4] Pegfilgrastim offers a much more convenient, but expensive, alternative to filgrastim. ■

References

1. Harris JM, et al. *Clin Pharmacokinet.* 2001;40(7): 539-551.
2. Neulasta Product Information. Amgen Inc. January 2002.
3. Holmes FA, et al. *J Clin Oncol.* 2002;20:727-731.
4. Lyman GH, et al. *Am J Med.* 2002;112(5):406-411.

CME Questions

30. IRS (aka metabolic syndrome) is:

a. obesity, increased serum cortisol, abnormal glucose homeostasis, and hypertension.
b. increased serum cortisol, abnormal glucose homeostasis, and hypertension.
c. abnormal glucose homeostasis, hypertension, dyslipidemia, and obesity.
d. hypertension, dyslipidemia, obesity, and increased serum cortisol.
e. dyslipidemia, obesity, increased serum cortisol, and abnormal glucose homeostasis.

31. Which one of the following questions is *false*?

a. Estrogen is one of the metabolites of testosterone.
b. Estrogen is not one of the metabolites of DHT.
c. Estrogen may be a necessary substrate for prostatic hypertrophy to occur.
d. The lack of estrogen metabolites when DHT is used does not have any potential disadvantages.

32. Causes of elevated amylase include all of the following *except*:

a. mumps and similar inflammatory disorders of salivary glands.
b. renal failure.
c. severe chronic sigmoid diverticulitis.
d. intestinal perforation.
e. macroamylasemia.

33. International physicians are widely aware of the relationship between *H pylori* and ulcer disease, and this has led to selection of appropriate therapies for eradication.

a. True
b. False

34. Elevations in amylase values as high as 3 times normal would be expected to occur in a significant number of patients with acute gastroenteritis.

a. True
b. False

Attention CME Subscribers

Due to an editorial error, a mistake has been made with the CME numbering. In the May 15, 2002 issue, questions 22-27 should be questions 24-29. A reminder will also be sent with your CME scantron. We regret any confusion this may have caused. ■

By Louis Kuritzky, MD

ACE Inhibitors, Muscle Strength, and Physical Functioning in Older Women

The use of angiotensin-converting enzyme (ACE) inhibitors has been shown in chronic systolic heart failure (CHF) to reduce mortality, and prevent progression from mild degrees of CHF to more severe disease. Additionally, ACEs have been shown to reduce mortality, stroke, and other vascular end points in persons with previous evidence of vascular disease (ie, adults > 55 with prior stroke, MI, peripheral vascular disease, or diabetes). Whether ACE can be of benefit in persons without CHF or proven vasculopathy was evaluated in this 3-year trial of hypertensive women (n = 641).

Subjects were divided into the categories of continuous ACE users (n = 61), intermittent users (n = 133), never users (n = 146), and "other users," whose hypertension had been controlled either continuously or intermittently with other drugs (n = 301).

Knee extensor muscle strength, walking speed, and overall physical activity was assessed. Mean age of the subjects was 78.9 years. Patients with CHF were *excluded* from the trial.

Over time, all groups lost some muscle strength, but the continuous ACE lost the least. There was a trend toward continuous ACE use being associated with lesser loss of muscle strength than intermittent ACE use. Walking speed (which has been shown to be predictive of disability and mortality, as well as other end points) also declined less in continuous ACE recipients than any other group.

Potential mechanisms by which ACE could favorably affect these end points include positive effect on myosin heavy chains in muscle, improvements in insulin sensitivity, improved skeletal blood flow due to reduced kinin breakdown, and others. ■

Onder G, et al. Lancet. 2002;359: 926-930.

Diagnosis of Pheochromocytoma—Which Test is Best?

Although a rare cause of hypertension (HTN), pheochromocytoma (PHEO) is ultimately correctable, and the potential devastating consequences of catecholamine excess found with PHEO merits consideration in a variety of clinical settings in which a secondary cause of HTN is suspect. Unfortunately, diagnosis is hampered by both false-negative and false-positive testing methodologies. Lenders and colleagues evaluated a variety of tests for PHEO in 865 patients submitted for PHEO evaluation at 4 referral centers over a 7-year period, of whom ultimately 214 were confirmed to have PHEO.

The tests studied included plasma free metanephrines (P-FMET), plasma catecholamines (P-CAT), urinary catecholamines (U-CAT), urinary total metanephrines (U-TMET), urinary fractionated metanephrines (U-FMET), and urinary vanillylmandelic acid (U-VMA).

The 2 measurements with highest sensitivity for PHEO were P-FMET and U-FMET. Highest specificity was found for U-VMA and U-TMET. Based on this information, Lenders et al conclude that P-MET should be the first test of choice for diagnosis of PHEO. Indeed, they suggest that the practice of ordering multiple diagnostic tests should be eschewed, indicating that the diagnosis of PHEO may be adequately included or excluded by simply using the P-FMET alone. ■

Lenders JWM, et al. JAMA. 2002;287: 1427-1434.

Sexual Dysfunction in Women with Type 1 Diabetes

The association of diabetes mellitus (DM) with erectile dysfunction is clearly established. Less studied is the relationship between diabetes and female sexual dysfunction (FSD). Enzlin and colleagues evaluated sexual function in 97 diabetic Belgian women using questionnaires to assess psychological adjustment to DM, marital satisfaction, depression, and sexual function. As controls, healthy nondiabetic age-matched women (n = 180) attending an outpatient gynecology clinic responded to the same questionnaire.

Almost twice as many DM women suffered than controls and reported sexual dysfunction (27% vs 15%). Specifically, arousal problems (indicated by poor lubrication) were more frequent, in contrast to disorders of desire, dyspareunia, and orgasm, which were found with equal frequency in the DM and control groups.

The population studied was young (mean age 34), so this prevalence of sexual dysfunction may appear surprising. Additionally, DM women with FSD were found to have a more negative appraisal of their DM, including more problems with emotional adjustment. DM women have a greater burden of FSD than age-matched counterparts. This is the largest study performed to date to compare the frequency of FSD in patients with and without DM. ■

Enzlin P, et al. Diabetes Care. 2002; 25:672-677.

In Future Issues:

Treating Onychomycosis: A Head-to-Head Comparison of Terbinafine and Itraconazole