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Pharmacologic Calvinism: Why Drugs Should Be Used for Indications, Not Side Effects

ABSTRACT & COMMENTARY

Synopsis: *Diphenhydramine was associated with significantly increased risk of inattention, disorganized speech, altered consciousness, urinary retention, and increased length of stay in hospitalized patients older than 70 years.*

Source: Agostini JV, et al. *Arch Intern Med.* 2001;161:2091-2097.

Agostini and colleagues, who were funded by the National Institute of Aging, undertook a prospective study of adverse effects of diphenhydramine (Benadryl) in hospitalized patients older than the age of 70 years. They hypothesized that this anticholinergic medication would increase symptoms of delirium in this vulnerable group. Four hundred twenty-six patients were prospectively enrolled. Of the 426 patients, 114 (27%) of them received diphenhydramine. This medication was prescribed as a hypnotic 68% of the time. For 21% of the time, it was administered for transfusion prophylaxis, and 3% of the time, it was given for allergies or for pruritis. The 114 patients who received diphenhydramine and the 312 who did not were similar in all the important variables, including age, Mini Mental Status Exam Score (MMSE), baseline sleeping difficulty, number or medications prior to admission, gender, and impairment in activities of daily living. Those who got diphenhydramine had statistically significant increases in delirium symptoms (relative risk [RR], 1.7; confidence interval [CI], 1.3-2.3), MMSE decline > 3 points (RR, 1.8; CI, 1.0-3.2), altered consciousness (RR, 3.2; CI, 1.6-6.1), abnormal psychomotor activity (RR, 2.3; CI, 1.2-3.3), behavioral disturbance (5.6, 1.0-29.9), and inattention (RR, 3.0; CI, 1.5-5.9) compared with baseline. Cognitive assessments were carried out by investigators blinded both to the study hypothesis and to the patients' diphenhydramine use. Patients who received diphenhydramine also had increased length of stay (7 vs 6 days) and a greater likelihood of urinary catheter placement (RR, 2.5; CI, 1-6). The risk of adverse effects increased in a dose-dependent manner.

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INSIDE

Agostini et al also found that about a quarter of diphenhydramine doses were administered inappropriately (eg, to those with known urinary retention or with no known history of transfusion reaction).

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

A large majority of patients who received diphenhydramine in this study got it as a sleeping aid, prescribed while they were in the hospital. The issue of sleep disturbance and sleeping pills in the elderly is like the elephant in the room that nobody wants to talk about. In this study and others,[1] about half of the older patients had baseline sleeping difficulty. Sleep, like most everything else, deteriorates with aging. The response of many clinicians is what Dr. Wallace Mendelson has referred to as "Pharmacologic Calvinism."[2] Instead of treating sleeping difficulty with any of the available effective hypnotics, many clinicians use antihistamines, antipsychotics, or antidepressants for their side effect of somnolence. I think there are 2 problems with this: 1) antihistamines, antipsychotics, and antidepressants are not as effective in inducing sleep as are hypnotics (especially the newer agents); and 2) in general, antihistamines, antipsychotics, and antidepressant drugs have more side effects than the newer hypnotics.

In the standard text of sleep medicine, Roehrs and Roth say, "Although studies have shown that H 1 antihistamines do increase sleepiness in healthy normal individuals, no studies have clearly established the dose range over which hypnotic effects in people with insomnia might be found. Low-dose antidepressants have also been used as hypnotics. It is the sedating side effect of the drug that is being sought. However, the antidepressants have cardiotoxic side effects and anticholinergic side effects that make this class of drugs a poor choice as a hypnotic in the absence of clinical depression."[3]

Walsh and Schweitzer recently reported that: 1) pharmacologic treatment of insomnia fell dramatically from 1987 to 1996; and 2) the use of antidepressants to treat insomnia has grown substantially.[4] Trazodone is a "prime offender" in this category. They present evidence that the use of antidepressants in insomnia has grown because of concern about dependence rather than because of recognition and treatment of depression in those reporting insomnia. Trazodone is associated with significant side effects, including daytime somnolence, orthostatic dizziness/hypotension, and priapism.[5,6] Further, trazodone appears to improve sleep in the nondepressed patient only in the short term and is less effective than newer hypnotic agents, such as zolpidem.[7]

We used to undertreat pain, and now make aggressive attempts to identify and relieve it appropriately. I suspect that in the not too distant future, we will look back on our currently poor job of addressing very treatable sleep disturbances in the same way. ❖

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The ESR or CRP— An Old Debate Flares Up

ABSTRACT & COMMENTARY

Synopsis: *The erythrocyte sedimentation rate (ESR) is affected by so many extrinsic factors that its clinical usefulness is severely compromised.*

Source: Jurado RL. *Clin Infect Dis.* 2001;33:548-549.

The erythrocyte sedimentation rate (esr) is a nonspecific screening test for various inflammatory diseases and has a long and venerable history. The test requires blood to be drawn and collected in citrate or EDTA as anticoagulant, is quick and inexpensive, and usually offered as part of the basic service. Although simple to perform, the ESR is the result of a complex biological process dependent upon the amount of fibrinogen (also an acute-phase reactant) and the degree to which red blood cells aggregate, which in turn depends upon the physical properties of the surface including free energy, charge, and dielectric constant.

Besides elevated concentrations of fibrinogen, the ESR is also increased by a variety of factors and reduced by others (*see Table*).

By contrast, the acute-phase reactant C-reactive protein (CRP) is not affected by any of these factors and is regarded as a better alternative for gauging the intensity of the inflammatory response and for providing a better means of monitoring. However, ESR is still preferred by some because, although CRP might be a better test, it requires specialized technology making it less widely available, takes longer to do, and is more expensive. Jurado dismisses these arguments claiming that those who still insist on using the ESR only do so because of their adherence to tradition and not because of science or logic.

COMMENT BY J. PETER DONNELLY, PhD

It may seem strange that this article should appear at this time in an infectious diseases journal, especially as the ESR has long given way to CRP in this area. However, while microbiologists and infectious disease physicians might be convinced that this debate (which has raged since the mid-1960s) has long been settled, other clinical specialists clearly think otherwise. Indeed, only recently a study was done among patients with solid tumors and lymphomas to investigate the possibility of using the ESR and CRP for differentiating neoplastic fever from infectious fever and concluded that neither was useful.[1]

Ironically, although CRP is a more specific acute-phase reactant than ESR, it still has to find its proper place in the clinic. After all, like the ESR, an elevated CRP level only reflects active inflammation but sheds no light upon the etiology. Its clinical use also depends upon the context and its ability to increase or lower diagnostic probabilities. Taken in isolation and without a clear purpose, neither the ESR nor CRP for that matter will be anything but a waste of time and money. ❖

Table

Factors Other Than the Concentration of Fibrinogen That Affect the ESR

Cause elevation of ESR	Cause reduction in ESR
Anemia	Morphological abnormalities of the red blood cells
Increased concentrations of other proteins including M-protein, macroglobulins, and RBC agglutinins	Polycythemia
Renal failure	High white blood cell count
Heparin	Hypofibrinogenemia
High blood cholesterol	High serum concentrations of bile salts that affect red blood cell membranes
Extreme obesity	Congestive heart failure
Female gender	Valproic acid
Advanced age	Low molecular weight dextrans
Tilting the tube	Cachexia
High temperature	Low temperature
	Delay > 2 h before testing
	Clotting
	Vibration

Reference

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Dr. Donnelly is Clinical Microbiologist, University Hospital, Nijmegen, The Netherlands.

Symptoms Associated with Hypersensitivity to Gastric Distention in Functional Dyspepsia

ABSTRACT & COMMENTARY

Synopsis: *Hypersensitivity to gastric distention is present in a subset of dyspeptic patients, and this finding will ultimately affect the diagnosis of such patients as well as provide a rationale for more effective therapy.*

Source: Tack J, et al. *Gastroenterology.* 2001;121:526-535.

Functional dyspepsia is a syndrome that includes chronic upper abdominal discomfort with no anatomic basis. Eating frequently provokes dyspeptic symptoms that may entail epigastric pain or burning, bloating, early satiety, eructations, nausea, and vomiting. Many speculations exist regarding potential pathophysiology for dyspepsia including *Helicobacter pylori* infection, gastric and/or intestinal motor abnormalities, central nervous system dysfunction, and visceral hypersensitivity. Previous studies have demonstrated sensitivity to gastric distention in many dyspeptic patients, but there has been no certainty that these findings were related to symptom etiology. This study evaluated 80 healthy controls and 160 patients with functional dyspepsia (symptomatic for at least 12 weeks in the last 12 months). No anatomic basis for dyspepsia was present in the patients, and esophageal acid exposure was normal. A distending balloon capable of measuring pressures and compliance was used to distend the stomach in all participants. Gastric emptying studies were performed with a ^{14}C octanoic acid breath test. Results indicated that dyspeptic patients were more sensitive to distention than the controls, and accommodation to the distending balloon was less in patients. It was found that 37% of all dyspeptic patients studied were hypersensitive. Symptoms associated with documented hypersensitivity included postprandial pain, belching, and weight loss.

COMMENT BY MALCOLM ROBINSON, MD, FACP, FACG

Dyspepsia can be a difficult clinical problem. It is extremely difficult to know exactly how aggressive we should be with diagnosis, and guidelines for therapy have been similarly obscure. Understanding the basis for any illness seems important for refining diagnoses and for selection of optimal therapy. This study, elegantly performed by the superb team of Tack and colleagues in Leuven, Belgium, helps us to understand dyspepsia in a significant subset of patients. For individuals with this type of dyspepsia, therapy should undoubtedly be focused on lessening the hypersensitivity present. Promotility agents and acid inhibitors would not be helpful in these patients, and we currently might try tricyclic and other antidepressants and perhaps the next generation of $5HT_3$ antagonists similar to the recently released and withdrawn alosetron will also provide relief for these troubled patients and their physicians. ❖

Cardiovascular Complications of Cocaine Use

ABSTRACT & COMMENTARY

Synopsis: *Cocaine is the most commonly used illicit drug among subjects seeking care in hospital emergency departments or drug-treatment centers. In addition, it is the most frequent cause of drug-related deaths reported by medical examiners.[1] In 1999, an estimated 25 million Americans admitted that they had used cocaine at least once; 3.7 million had used it within the previous year; and 1.5 million were current users. During the same year, cocaine was mentioned in 30% of all drug-related visits to emergency departments.[1] As cocaine abuse has become widespread, the number of cocaine-related cardiovascular events, including angina pectoris, myocardial infarction, cardiomyopathy, and sudden death from cardiac causes, has increased dramatically.*

Source: Lange R, Hillis D. *N Engl J Med.* 2001;345:351-358.

Lange and hillis have written an excellent review article regarding the epidemiology of cocaine use, the pharmacology and mechanisms of action, and the varied deleterious effects of cocaine on different systems of the body.

Mechanism of Action

Cocaine blocks the presynaptic reuptake of norepinephrine and dopamine, producing an excess of these neurotransmitters at the site of the postsynaptic receptor. In short, cocaine acts as a powerful sympathomimetic agent.

Cocaine-Related Myocardial Ischemia and Infarction

Of patients who come to the emergency department with nontraumatic chest pain, 14-25% in urban hospitals and 7% in suburban hospitals have detectable levels of cocaine or cocaine metabolites in their urine.[2]

Most patients with cocaine-related myocardial infarction (MI) are young, nonwhite, male cigarette smokers without other risk factors for atherosclerosis who have a history of repeated use of cocaine. About half the patients with cocaine-related MI have no evidence of atherosclerotic coronary artery disease on subsequent angiography.[3]

The accurate identification of patients with cocaine-related MI may be difficult for at least 2 reasons. First, the electrocardiogram may be abnormal in many patients with chest pain after cocaine use, even in the absence of MI. The second reason is that serum creatine kinase concentrations are elevated in about half of cocaine users, who do not have MI, due to rhabdomyolysis.[4] Accordingly, serum troponin concentrations are used.

The recently revised guidelines of the American Heart Association for emergency cardiovascular care[5] recommend nitroglycerin and benzodiazepines as first-line agents for patients with cocaine-related MI or infarction and phentolamine as a second-line agent; propranolol is contraindicated. Thrombolysis is not recommended unless evidence of evolving MI persists despite medical therapy and an occluded coronary artery is shown to be present on angiography. Thrombolysis is contraindicated if uncontrolled, severe systemic arterial hypertension is present.

Cocaine, Cigarette Smoking, and Alcohol Use

The deleterious effects of cocaine on myocardial oxygen supply and demand are exacerbated substantially by concomitant cigarette smoking. This combination markedly increased the product of the heart rate and systemic arterial pressure, a value that determines myocardial oxygen demand, while simultaneously decreasing the diameter of diseased segments of the coronary arteries.

Among those with abuse of multiple substances who are seen in emergency departments, the combination of cocaine and ethanol is the most common.[1] It is the second most common combination in patients who die of substance abuse, accounting for more than 1000 deaths per year.

Cocaine-Induced Myocardial Dysfunction

Long-term cocaine abuse has been reported to cause left ventricular hypertrophy[6] and systolic dysfunction. Several reports have described dilated cardiomyopathy in long-term cocaine abusers, as well as reversible, profound myocardial depression after binge cocaine use.

Cocaine-Induced Dysrhythmias

The cardiac dysrhythmias ascribed to cocaine have occurred in the context of profound hemodynamic or metabolic derangements, such as hypotension, hypoxemia, seizures, or MI. Nonetheless, because of cocaine's sodium-channel-blocking properties and its ability to induce an enhanced sympathetic state, it is considered likely to produce or exacerbate cardiac arrhythmias, particularly under certain pathologic conditions. The development of lethal arrhythmias with cocaine use may require a substrate of abnormal myocardium.

Lidocaine has been used safely in patients with cocaine-induced ventricular tachycardia or fibrillation. Class IA antiarrhythmic drugs, such as quinidine, procainamide, and disopyramide, should be avoided, since they may exacerbate prolongation of the QRS and QT intervals and slow the metabolism of cocaine and its metabolites.

Endocarditis

The elevation of the heart rate and systemic arterial pressure that accompanies cocaine use may induce valvular and vascular injury that predisposes users to bacterial invasion. The immunosuppressive effects of cocaine may increase the risk of infection. Alternatively, the manner in which cocaine is manufactured, as well as the adulterants that are often present in cocaine, may increase the risk of endocarditis. In contradistinction to endocarditis associated with other drugs, the endocarditis associated with cocaine abuse more often involves the left-sided cardiac valves.[7]

Aortic Dissection

Aortic dissection or rupture has been temporally related to cocaine use and should, therefore, be considered as a possible cause of chest pain in cocaine users. Dissection probably results from the substantial increase in systemic arterial pressure induced by cocaine. In addition to aortic rupture, cocaine-related

rupture of mycotic and intracerebral aneurysms has been reported.

COMMENT BY DAVID OST, MD, FACP, & NAJMA USMANI, MD

Cocaine use continues to increase. As a result, the number of cocaine-related visits to emergency departments, hospitalizations, cardiovascular complications, and deaths has risen dramatically. The understanding and early recognition of cocaine-related cardiovascular complications are essential to their proper management. The possibility of cocaine use should be considered in young patients with myocardial ischemia or infarction, arrhythmias, myocarditis, or dilated cardiomyopathy. ❖

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Pharmacology Update

Cefditoren Pivoxil Tablets—A New Cephalosporin

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

Cefditoren is a new semisynthetic "third/fourth generation" cephalosporin recently approved by the FDA. It has good antimicrobial activity against common pathogens of the respiratory tract such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. TAP Pharmaceuticals licensed cefditoren pivoxil from a Japanese pharmaceutical company. The drug has been in wide use in Japan for 7 years, where 41 million prescriptions have been dispensed. Cefditoren is marketed by TAP as Spectracef.

Indications

Cefditoren is indicated for use in adults or adolescents for the treatment of the following infections: acute bacterial exacerbation of chronic bronchitis caused by *H influenzae*, *Streptococcus parainfluenzae*, *S pneumoniae*, or *M catarrhalis*; pharyngitis/tonsillitis caused by *Streptococcus pyogenes*; uncomplicated skin and skin-structure infections caused by *Staphylococus aureus*, or *S pyogenes*.[1]

Dosage

The recommended dose for acute bacterial exacerbation of chronic bronchitis is 400 mg twice daily for 10 days. For pharyngitis/tonsillitis or uncomplicated skin and skin structure infections, the dose is 200 mg twice daily for 10 days. The drug should be taken with meals to improve absorption. It should not be taken with antacids, histamine-2 receptor antagonists, and, possibly proton pump inhibitors. No dose adjustment is required in patients with mild renal impairment or mild-to-moderate hepatic impairment.[1]

Potential Advantages

Cefditoren has demonstrated in vitro activity against intermediate and penicillin-resistant strains of *S pneumoniae* as well as beta lactam and macrolide resistant *S pyogenes*.[1-3]

Potential Disadvantages

Cefditoren, as with other cephalosporins, is not active against atypical respiratory pathogens such as *Chlamydia pneumonia*, *Mycoplasma pneumoniae*, and *Legionella pneumophilia*. It is not recommended for long-term use as pivalate-containing compounds have been associated with carnitine deficiency when used over a period of months. Patients with milk protein hypersensitivity should not take cefditoren as the tablets contain sodium caseinate.[1] The most frequent side effect is diarrhea (12-14%) and the primary reason for discontinuation of therapy is diarrhea or nausea.

Approximately 2-3% of patients discontinue therapy.[1]

Comments

Cefditoren pivoxil is considered a "third/fourth" generation cephalosporin. It is administered as the prodrug (pivoxil) which is hydrolyzed by esterases after oral absorption. It has excellent in vitro activity against many

respiratory tract pathogens such as *S pneumonia*, *H influenzae*, and *M catarrhalis*. It is not active against atypical respiratory pathogens, *Pseudomonas aeruginosa* or *B fragilis*. Data from clinical trials indicate that the efficacy and safety of cefditoren are comparable to other similar antibiotics in the treatment of acute exacerbation of chronic bronchitis, pharyngitis, sinusitis, and uncomplicated skin and skin structure infections.[4,5] Comparative antibiotics included penicillin VK for pharyngitis, cefuroxime or clarithromycin for acute exacerbation of chronic bronchitis, cefadroxil or cefuroxime for uncomplicated skin and skin structure infections, and amoxicillin/clavulanate for acute maxillary sinusitis.

Cefditoren is expected to be launched in December. Costs are not available at this time.

Clinical Implications

Cefditoren appears to be safe and efficacious for approved indications but does not appear to offer any clear clinical advantages over available agents. It is currently not approved for community-acquired pneumonia or sinusitis. Antibiotic resistance is regarded by several expert committees as a major public health threat. Misuse and overuse of antibiotics is considered a major driver.[7] Therefore, judicious use of cefditoren or any antibiotic is essential. ❖

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CME Questions

37. The use of diphenhydramine in hospitalized older patients:
a. improved subjective sleep quality with no increase in side effects.
b. was associated with severe orthostatic hypotension in 10% of patients.
c. was most commonly prescribed to prevent transfusion reactions.
d. was associated with increased risk of cognitive decline.
e. occurred in more than 50% of such patients.

38. All of the following factors lead to a spurious ESR *except*:
a. anemia.
b. high white blood cell count.
c. low molecular weight dextrans.
d. citrate anticoagulant.
e. tilting the tube.

39. Dyspepsia with visceral hypersensitivity manifested by pain with gastric distention is associated with all of the following symptoms *except*:
a. nausea.
b. bloating.
c. early satiety.
d. diarrhea.
e. upper abdominal pain and/or burning.

40. Which of the following class of drugs contraindicated in cocaine-induced myocardial ischemia?
a. Calcium channel blockers
b. Beta Blockers
c. Diuretics
d. Nitrates
e. None of the above

41. Cocaine:
a. is the most commonly used illicit drug among subjects seeking care in hospital emergency departments or drug-treatment centers.
b. is the most frequent cause of drug-related deaths reported by medical examiners.
c. acts as a powerful sympathomimetic agent.
d. All of the above

42. Which one of the following statements is correct?
a. The most uncommon side effect of cefditoren is diarrhea.
b. Patients with milk protein hypersensitivity should not take cefditoren as the tablets contain sodium caseinate.
c. Cefditoren should not be taken with meals.
d. Cefditoren is recommended for long-term use.
e. None of the above

By Louis Kuritzky, MD

Lack of Health Insurance and Decline in Overall Health In Late Middle Age

It is intuitive that uninsured Americans would use fewer healthcare services. Whether insurance status is related to overall health in late middle age is little studied. As many as 1 in 6 persons age 55-64 are uninsured in the United States. Baker and colleagues examined the health status of persons included in the Florida Health and Retirement Survey Database (n = 9824) as observed over a 4-year time period. Over the study period, 79.6% were continuously insured, 10.9% intermittently insured, and 9.5% continuously uninsured.

Uninsured persons were 2-2.5 times more likely to report a major decline in overall health, more heavily weighted among those continuously uninsured. New difficulties with mobility (eg, walking or stair-climbing) were also more common in uninsured individuals.

The deleterious effects of uninsured status were not related to gender, ethnicity, or income, but better baseline health was associated with greater risk for major decline in health status among the uninsured. The number of persons uninsured over age 55 is increasing. The observation that uninsured status increases the likelihood of negative health outcomes is concerning. ❖

Baker DW, et al. N Engl J Med. 2001; 345:1106-1112.

Long-Term Weight Loss with Sibutramine

The burgeoning epidemic of obesity and its consequences shows no signs of diminution. Currently available pharmacotherapy tools have enjoyed only modest use in the clinical setting. Long-term trials are necessary to convince the physician and patient populations that pharmacotherapy of obesity is meritorious. This 1-year trial of obese adults (BMI > 30) used sibutramine 15 mg on a daily continuous or daily intermittent schedule vs. placebo. The intermittent schedule used a 7-week hiatus of pharmacotherapy after each 3-month segment, based upon the observation that weight reductions tend to slow after this interval.

Subsequent to the 4-week run-in period, at 1 year patients on treatment lost a mean of 4% of their body weight (continuous regimen) and 3.5% on the intermittent schedule, both of which results were significantly greater than placebo. Although sibutramine has been reported to be associated with changes in blood pressure, no blood pressure changes were seen during the study period in this population. Sibutramine is effective in long-term (1 year) management of obesity. ❖

Wirth A, Krause J. JAMA. 2001;286: 1331-1339.

Prediction of All-Cause and Cardiovascular Mortality in Elderly People from One Low Serum Thyrotropin Result

Subclinical hyperthyroidism (SCH) is defined as a subnormal TSH level accompanied by normal levels of T4 and T3; as is implied in the name designation, persons must also be free of symptoms of hyperthyroidism. The pathologic consequences (or lack therof) have been thus far ill-defined. Parle and colleagues evaluated the impact of SCH upon mortality in a large population (n = 1191) of persons older than age 60 followed for up to 10 years (mean follow-up, 8.2 years). Of the study population, 6% fulfilled diagnostic criteria for SCH.

All-cause mortality was significantly increased at years 2, 3, 4, and 5 after study entry for those with SCH, mostly due to an increased risk of death from circulatory diseases. Earlier reports have indicated an increased risk of atrial fibrillation in persons with SCH. Parle et al suggest that persistently low TSH levels in asymptomatic persons with normal levels of T4 and T3 are indicative of increased mortality risk; whether reducing T4 or T3 levels to a point where TSH is normalized will reduce risk of mortality is not yet known. ❖

Parle JV, et al Lancet. 2001;358: 861-865.

In Future Issues: What Does a Low Cholesterol Mean?