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INSIDE

Human Bites: Facts and Fiction

ABSTRACT & COMMENTARY

Synopsis: *Infection rates in low-risk human bites are exceedingly low. Antibiotic treatment may not be necessary for these patients.*

Source: Broder J, et al. *Am J Emerg Med*. 2004;22:10-13.

THIS STUDY WAS AIMED AT EVALUATING THE NEED FOR ANTIBIOTIC therapy in low-risk human bite wounds. It was designed as a prospective, placebo-controlled, double-blinded study and was performed over a 4-year period of time at a major academic urban emergency department. Those patients that had human bites were eligible for inclusion except those who had them in high-risk areas (ie, hands, feet, cartilaginous structures). Patients were also excluded if they had puncture wounds or any wound that was penetrating deeper than the epidermis. Those patients sustaining low-risk human bite wounds were assigned by Broder and associates into either the placebo group or a 5-day course of antibiotics (cephalexin/penicillin).

Patients were instructed to return at 48 and 96 hours after their initial visit to the emergency department. Assessment for signs of infection including erythema, warmth, tenderness, lymphangitis, induration, purulent discharge and fever were documented. Means, proportions, and 95% confidence intervals were use to analyze and detect differences between both groups.

A total of 127 patients were enrolled in this study and 125 of them completed the study protocol. The median age was 32 years. Infection developed in only one of the 62 patients that received the placebo and none of the 63 patients that received the antibiotic. No difference was found between the medication compliance among the groups. Broder et al suggest limiting antibiotic usage for those patients with low-risk human bite wounds.

COMMENT BY JOSEPH VARON, MD, FACP, FCCP, FCCM

Human bites are quite common. Indeed, it has been estimated that nearly half of all people in this country will experience a canine, feline or human bite during the course of their lifetimes.[1] The cost of treating these patients is also exceedingly high and estimated at 100 million US dollars per year.[2]

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The study by Broder et al is important as it presents interesting and compelling data against the routine use of antibiotics for low-risk human bites.[3]

Most standard textbooks still recommend antibiotic treatment routinely for all human and nonhuman bites. The 1.6% risk of infection in the placebo group is substantially lower than what has previously been reported. This study supports a change in practice standards for low-risk human bites. However, the reader must understand that most patients in this study had superficial abrasion or dental impressions. Prior studies have reported a substantially higher rate of infections, mostly because they involved puncture wounds and lacerations.[4]

Clinicians caring for patients with low-risk human bites must consider each patient individually and based on the results of the study by Broder et al, withhold antibiotic therapy as long as close follow up is available. ■

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Dr. Varon is Professor at the University of Texas Health Science Center, Houston Tex.

Helicobacter pylori Infection and Eradication on Heartburn and Gastroesophageal Reflux

ABSTRACT & COMMENTARY

Synopsis: *Eradication of* H. pylori *in a large outpatient general practice setting seemed to protect against the subsequent onset of gastroesophageal reflux disease (GERD), and there was evidence that eradication of* H. pylori *neither improved nor worsened pre-existing GERD symptoms.*

Source: Harvey RF, et al. *BMJ*. 2004;328(7453):1417.

HARVEY AND COLLEAGUES STUDIED 10,537 PATIENTS in 7 general practices were invited to participate in a study of *Helicobacter pylori* incidence and the effects of its eradication. In this study, 1634 patients positive for *H. pylori* were compared to 3268 randomly selected *H. pylori*-negative controls. *H. pylori* positive patients were randomized to either clarithromycin-ranitidine bismuth citrate eradication therapy or to placebo. *H. pylori* infection was associated with a slight excess of heartburn prevalence at baseline. Although successful eradication therapy neither increased nor decreased heartburn prevalence, patients with regurgitation symptoms at baseline developed less heartburn over a 2-year follow-up period.

COMMENT BY MALCOLM ROBINSON MD, FACP, FACG

Harvey et al comment that the results of this study may be consistent with effects of the hypersecretion associated with *H. pylori* infection of the antrum. However, *H. pylori* infection is not that simple. Although some strains of *H. pylori* do lead to hypersecretion and

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sometimes to duodenal ulcer disease, these strains are apparently vanishing in the Western world. Other variants of *H. pylori* can lead to gastric atrophy and to decreased gastric acid secretion. Moreover, many experts believe that eradication of *H. pylori* can produce an impaired response to the therapeutic effects of proton pump inhibitors. Harvey et al readily admit the absence of endoscopic or physiologic data in these patients, but they believed that these potential study flaws are balanced by the large numbers of participants in the study, the randomized design, and the avoidance of prolonged acid suppression in this population as part of the treatment paradigm. It seems to this reviewer that there remain more questions than answers in this area. Epidemiologic data strongly suggest a protective effect of *H. pylori* infection against GERD. There are a number of studies that have shown increased GERD prevalence after *H. pylori* eradication. Perhaps most importantly, there was no medical justification for the strategy undertaken in this study since eradication of *H. pylori* in normal individuals or GERD or dyspepsia cannot currently be justified by an evidence based medical data. ■

Much More About CRP!

ABSTRACTS & COMMENTARY

Synopsis: *CRP values as a continuous variable have independent predictive value for subsequent coronary events in apparently healthy women.*

Sources: Ridker PM, Cook N. *Circulation*. 2004;109: 1955-1959; Verma S, et al. *Circulation*. 2004;109:2058-2067; Verma S, et al. *Circulation*. 2004;109:1914-1917; Khreiss T, et al. *Circulation*. 2004;109:2016-2022.

In a new analysis by Ridker from the large Women's Health Study, levels of C-reactive protein (CRP) at baseline were correlated with first cardiovascular events over a 9-year period. The particular focus of this report was very low and very high CRP levels, as well as looking at deciles of baseline CRP with and without adjustment for diabetes and Framingham Risk Score. In this study, 28,000 low-risk women were evaluated at entry, who were "similar to that of the general population in terms of . . . lipid levels . . . and metabolic syndrome." Framingham Risk Scores (FRS) were computed and analyses were carried out adjusted for both FRS and diabetes.

A graded relative risk was demonstrated for each of 10 CRP groups, all highly statistically significant. Thus, CRP has again been shown to have an independent predictive value on subsequent events in patients without clinical CAD. The analysis of very low (< 0.5 mg/L and very high (> 10 mg/L) levels correlate with both crude and FRS adjusted risk groups. Thus, unadjusted event rates were 6-fold higher in individuals with an initial CRP > 10 compared to an initial CRP < 0.5; adjusted rates in FRS and diabetes were 2-fold higher for CRP >10 mg/L. In fact, even between 0.5 and 1.0 mg/L there was a near doubling of adjusted risk. The authors conclude that "there is no evidence . . . of any threshold affect." They also point out that unusually low or unusually high values generally do not represent false negatives or positives. They believe that actual CRP levels provide considerable value over and above the recommended cut points of < 1, 1-3, and > 3 established by the recent CDC/AHA guidelines for use CRP. Although the highest CRP group (> 10 mg/L) represented only 5.5% of the total population, their risk was strikingly elevated. Those women with levels of > 20 at baseline (2.2% of the total population) were at an even greater risk. Fifteen percent of the population had an initial level of < 0.5 with an extremely low event rate. The authors conclude that CRP may play a direct role in atherothrombosis, given the precisely graded increases in risk across 9 cut points, and that at very high CRP levels, the increased CV risk is consistent with the hypothesis that CRP may have direct vascular effects. They furthermore suggest that the data supports the concept that chronic inflammatory states, such as arthritis, periodontal disease, etc, may be disposed to increased CV events, rather than high CRP being considered a false positive response. Furthermore, the authors emphasize that only a high sensitivity assay should be used for evaluation of CRP and two measurements are recommended for any level of > 10 mg/L.

COMMENT BY JONATHAN ABRAMS, MD

This report, and many others, link vascular events to gradations of CRP. CRP has been studied in many different populations and the data are consistent. The marked differential of risk between very low and very high CRP levels suggests a pathogenetic role for CRP itself. An in vitro basic science report from Canada suggests that CRP may have an adverse effect on endothelial progenitor cells (EPC) which are believed to be responsible for (favorable) neovascularization and angiogenesis. Investigators found that adding CRP to the experimental medium reduced EPC cell counts, inhibited the expression in specific endothelial cell markers, and increased endothelial cell apoptosis. Angiogenesis was impaired and endothelial nitric

oxide synthase expression was diminished. Of great interest, the diabetes drug, rosiglitazone, attenuated these effects. These authors concluded that CRP (in this case, human recombinant CRP) has inhibitor effects on EPC differentiation, survival, and function, and thus may decrease the angiogenesis response to chronic ischemia. Verma et al conclude that CRP should now be seen as a "prominent partaker in endothelial dysfunction and atherosclerosis." Verma et al address conformational modification of CRP, such that differing subunits of CRP can have a greater or lesser pro-inflammatory phenotype, which may modulate subsequent cardiovascular risk. Furthermore, they emphasize a wide variety of cellular effects in multiple experiments which support a direct role of CRP in promoting endothelial dysfunction and a variety of pro-inflammatory and pro-atherosclerotic actions. Transgenic animals that can express human CRP have been developed; these mice are prothrombotic and atherogenic, and are associated with "adverse cardiovascular processes," including impaired NO production, and enhanced endothelin release. These authors suggested that in the future, strategies to decrease CRP and modify its structure may become available to modulate atherosclerotic plaque initiation, progression, and rupture.

Although considerable controversy remains regarding the putative role of CRP as a participant or a marker for adverse cardiovascular events, it appears that there is a great deal of evidence that C-reactive protein itself, particularly with certain structural conformational profiles, can become pro-inflammatory. Thus, the hypothesis shared by many but not all, strongly supports an active role of CRP in the early as well as late atherothrombotic process. It is well-known that LDL cholesterol lowering results in decreased CRP levels; other interventions that reduce CRP itself may result in decreased atherothrombosis ". . . and that a virtual absence of CRP may in fact be protective." CRP can be produced within vascular vessel muscle of diseased coronary arteries in addition to the liver. While many of these basic science reports have no direct effect on clinical practice as yet, it does appear that CRP status, either directly or as a surrogate for an inflammatory state, is a valid and important construct relating to both healthy as well as unhealthy arteries. ■

Dr. Abrams is Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque.

Laparoscopy for Primary Colorectal Cancer Resection

ABSTRACT & COMMENTARY

Synopsis: *In a prospective, randomized trial, primary excision of colorectal carcinomas by laparoscopic surgery was compared with laparotomy. Disease recurrence and 5-year survival were not significantly different in the 2 groups. Operative time was greater for those receiving laparoscopic approach but post-operative recovery and hospital stays were shorter.*

Source: Leung KL, et al. *Lancet*. 2004;363:1187-1192.

THE PRIMARY SURGICAL APPROACH TO COLORECTAL carcinoma remains the single greatest chance of cure. Laparoscopic resection of this disease has been used since 1991 and it has been shown to improve post-operative recovery and reduce surgical stress. However, due to concerns regarding the adequacy of disease control and long-term survival, this procedure is only recommended for colorectal cancer as part of a clinical trial. Leung and colleagues from the Department of Surgery at the Chinese University of Hong Kong conducted a randomized controlled clinical trial with the goal of demonstrating that the survival rates are similar after laparoscopic and open resection for rectosigmoid carcinoma. Between 1993 and 2002, 403 patients with rectosigmoid cancer seen at the Prince of Wales Hospital and the United Christian Hospital in Hong Kong were randomized to receive either laparoscopic assisted (n = 203) or conventional open (n = 200) sigmoid colectomy. Disease-free interval and overall survival were analyzed post-operatively.

After curative resection, the 5-year survival rate for the laparoscopic group was slightly greater than that of the open resection group (76.1% vs 72.9%). However, patients in the laparoscopic resection group had a slightly lower probability of being disease free at 5 years than those in the open resection group (75.3% vs 78.3%), but neither of these findings was significant. The postoperative recovery for the laparoscopic group was significantly better, but the operative time for the laparoscopic procedure was significantly longer and the direct cost was greater. The overall morbidity and operative mortality was the same between the 2 groups.

■ COMMENT BY WILLIAM B. ERSHLER, MD

Laparoscopic surgical procedures have evolved dramatically over the past decade and, at many sites, have supplanted the need for open surgeries and the inherent

associated costs in terms of postoperative morbidity and lengthy recovery. The concern that appropriate wide excision and regional node sampling would be compromised by the procedure has delayed its widespread use for primary colon cancer surgery. In the current randomized clinical trial the results of laparoscopic excision were analogous to open laparotomy in terms of disease recurrence and overall survival. Thus, it would seem perfectly reasonable to recommend this approach.

However, when it comes to changing standing surgical approaches in oncology, the pace is very slow. Take for example how long it took for surgeons to abandon the radical mastectomy in favor of the modified mastectomy or even lumpectomy (with axillary node sampling). Thus, despite this relatively large trial published in a first-line journal, it would be surprising to see surgeons abandon their standard approach. Furthermore, the results from this single institution at which the participating surgeons obviously have extensive experience in laparoscopic techniques cannot readily be translated to community practice where the experience may be limited. Thus, the report is of great interest. Hopefully, surgical oncology training programs will evolve in such a way that this methodology will be familiar to a greater number of practicing surgeons and laparoscopic procedures will be considered for patients in whom such an approach is considered appropriate. ■

Dr. Ershler is an oncologist at INOVA Fairfax Hospital Cancer Center, Fairfax, VA; Director, Institute for Advanced Studies in Aging, Washington, DC.

Pharmacology Update

Rifaximin Tablets (Xifaxan™)

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

THE FIRST NONABSORBABLE, GASTROINTESTINAL-selective antibiotic has been approved for the treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli*. Rifaximin, a derivative of rifampin, is currently available in 17 countries worldwide. It is marketed in this country as Xifaxan™ by Salix Pharmaceuticals.

Indications

Rifaximin is indicated for the treatment of patients, 12 years or older, with travelers' diarrhea caused by noninvasive strains of *E. coli*. It should not be used for diarrhea complicated by fever, blood in the stool, or diarrhea caused by pathogens other than *E. coli*.[1]

Dosage

The recommended dose is 200 mg taken 3 times a day for 3 days. It may be taken without regard to meals. If the diarrhea persists more than 24-48 hours or if fever or blood in the stool occurs, rifaximin should be discontinued and medical attention should be sought.[1]

Rifaximin is supplied as 200 mg tablets.

Potential Advantages

Rifaximin is essentially not absorbed after oral administration as less than 0.4% is excreted in the urine. Adverse events during clinical studies were similar to placebo and rifaximin has been shown not to significantly affect intestinal or hepatic CYP3A4 activity.[1]

Potential Disadvantages

Rifaximin is only indicated for uncomplicated travelers' diarrhea caused by *E. coli*. Activity against other pathogens such as *Campylobactor jejuni*, *Shigella* spp., or *Salmonella* spp. has not been demonstrated.[1] Hypersensitivity reactions (eg, allergic dermatitis, angioneurotic edema, urticaria) have been reported in postmarketing studies outside the United States. Development of resistant strains of *E. coli* has been shown in vitro.[1] Common side effects are flatulence, headache, abdominal pain, rectal tenesmus, defecation urgency, nausea, constipation, pyrexia, and vomiting. However the frequencies of these were not different compared to placebo.[1]

Comments

Rifaximin is a virtually nonabsorbable semi-synthetic antibiotic. Its efficacy was studied primarily in Mexico, Central America, Africa, and India. The primary efficacy end point was time to last unformed stool (TLUS). Clinical cure was defined as absence of unformed stools. TLUS for rifaximin (600 mg daily for 3 days) was about 33 hours compared to about 60 hours for placebo.[1,2] Clinical cure was 79.2% and 60.5% respectively ($P = .001$).[1] In a comparative study, rifaximin (400 mg twice daily for 3 days) was comparable to ciprofloxacin (500 mg twice daily for 3 days).[3] The median TLUS were 25.7 hours and 25.0 hours respectively. Rifaximin also appeared to shorten the duration of unformed stools compared to trimethoprim/sulfamethoxazole.[4] The cost of rifaximin was not available at the time of this review.

Clinical Implications

Travelers' diarrhea is characterized by a twofold or greater increase in the frequency of unformed bowel movement and associated abdominal cramps, nausea, bloating, urgency, fever, and malaise.[5] It is generally acquired by ingestion of fecal contaminated food or water. An effective antibiotic treatment is ciprofloxacin (500 mg twice daily for 3 days). Treatment generally will shorten the duration of illness from 3-5 days to 1-1.5 days. Rifaximin provides an alternative for uncomplicated travelers' diarrhea caused by *E. coli* (enterotoxigenic and enteroaggregative strains). It may be less effective against enteroaggregative-negative strains.[6] It is not recommended for use in diarrhea caused by other pathogens such as *Campylobactor jejuni*, *Salmonella* spp., and *Shigella* spp. or in more severe diarrhea (ie, fever or blood in the stool). ■

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CME Questions

1. **The study done in Bristol, United Kingdom, indicated that the eradication of *H. pylori*:**
   a. increased GERD after successful treatment.
   b. dramatically improved GERD when *H. pylori* was successfully eliminated.
   c. had no effect on existing GERD, but seemed to prevent patients with regurgitation from developing heartburn over the next 2 years.
   d. prevented the development of gastric adenocarcinoma.
   e. led to increased esophageal adenocarcinoma in the patient whose *H. pylori* had been eliminated.

2. **CRP:**
   a. increases endothelial cell apoptosis.
   b. impairs angiogenesis.
   c. diminishes endothelial NO production.
   d. All of the above

Answers: 1 (c); 2 (d)

By Louis Kuritzky, MD

Prevention of Disabling and Fatal Strokes by Successful Carotid Endarterectomy in Patients without Recent Neurological Symptoms

CLEAR-CUT BENEFIT FROM CAROTID endarterectomy for secondary prevention of stroke amongst persons with carotid stenosis who have suffered a stroke/TIA has been well established. Less data is available to lead clinicians towards the best therapeutic choice in persons with asymptomatic carotid stenosis (aCST). The MRC Asymptomatic Carotid Surgery Trial studied patients (n = 3120) with at least 60% stenosis confirmed by ultrasound, in the absence of prior neurologic symptoms suggesting ischemia. Study subjects were enrolled beginning in 1993, and followed for up to 5 years.

When immediate perioperative stroke and death was excluded, the overall 5-year stroke risk was 3.8% in the operative group, versus 11% in the medically managed group. Even when including the perioperative stroke/death risk (= 3.1%), the overall 5-year risk profile supported carotid endarterectomy (stroke rate 6.4% vs 11.8%).

No particular subgroup was noted to have any greater or lesser benefit. For instance, similar benefits were seen in both genders, for all degrees of stenosis greater than 70%, and for all ages up to age 74. For those older than age 74, mortality benefits were notably absent, due to the overriding effect of deaths from other causes.

These data should enhance clinician confidence in the appropriateness of carotid endarterectomy for asymptomatic individuals with greater than 70% stenosis. A critical factor in the decision path will be whether any one clinician's local surgical outcomes are as excellent as those demonstrated here: a higher perioperative stroke/mortality rate could completely defeat long-term benefits. ■

MRC Asymptomatic Carotid Surgery Trial Collaborative Group. Lancet. 2004;363:1491-502

Cox-2 Inhibitors vs Nonselective NSAIDs and CHF Outcomes in Elderly Patients

USE OF NON-SELECTIVE NSAIDS CAN induce retention of Na+, K+, and water. Whether selective Cox-2 inhibitors (COXIBs) are fraught with an equally daunting likelihood of potential for fluid and electrolyte imbalance is uncertain. One large study of rofecoxib indicated an increased risk for acute MI, but the implication of these data is much debated. Because many senior adults are receiving either NSAIDs or COXIBs, the relative risk for induction of heart failure (CHF) by these classes of agents is important to discern.

To compare the likelihood of CHF in patients receiving COXIBs, as compared to NSAIDs, Mamdani and colleagues performed a population-based retrospective cohort study of adults over age 66 who had been prescribed rofecoxib (n = 14,583), celecoxib (n = 18,908), NSAIDs (n = 5391), and a control group (non-users of NSAIDs, n = 100,000).

The relative risk for CHF admission amongst recipients of NSAIDs and rofecoxib was increased compared to controls (RR = 1.8 and 1.4, respectively). Celecoxib use was not associated with an increased CHF risk vs control.

NSAIDs are confirmed to increase risk for CHF admission. Amongst COXIBs, celecoxib does not appear to be associated with the same increased CHF risk as rofecoxib.

Mamdani M, et al Lancet. 2004;363: 1751-1756.

Interventions for the Prevention of Falls in Older Adults

ONE-THIRD OF PERSONS OLDER THAN age 65, and one-half of those older than 80 sustain a fall annually, many of which result in hospital admission, impairment of mobility, or even death. A variety of interventions intended to reduce falls in the elderly have been studied, including exercise, environmental modification, education, and multifactorial risk identification and management.

Chang and associates performed a meta-analysis to evaluate comparative benefits of individual fall-prevention interventions and multifactorial fall risk assessment and management (MFRAM) programs, compared to usual care. A MFRAM was defined as a post-fall evaluation coupled with intervention recommendations and followup. Assessing data from 40 trials, an overall risk reduction of 12% was seen. Meta-regression of individual fall-reduction program components indicated that MFRAM was most effective (NNT = 11), followed by exercise interventions (NNT = 16).

The environmental modification or educational program components of fall prevention did not emerge with a statistically significant favorable effect upon falls. The best investment of effort for fall prevention in seniors appears to be MFRAM and exercise.

Chang JT, et al BMJ USA. 2004;4:223-226.

"Torsades Fabriquées"?

By Ken Grauer, MD

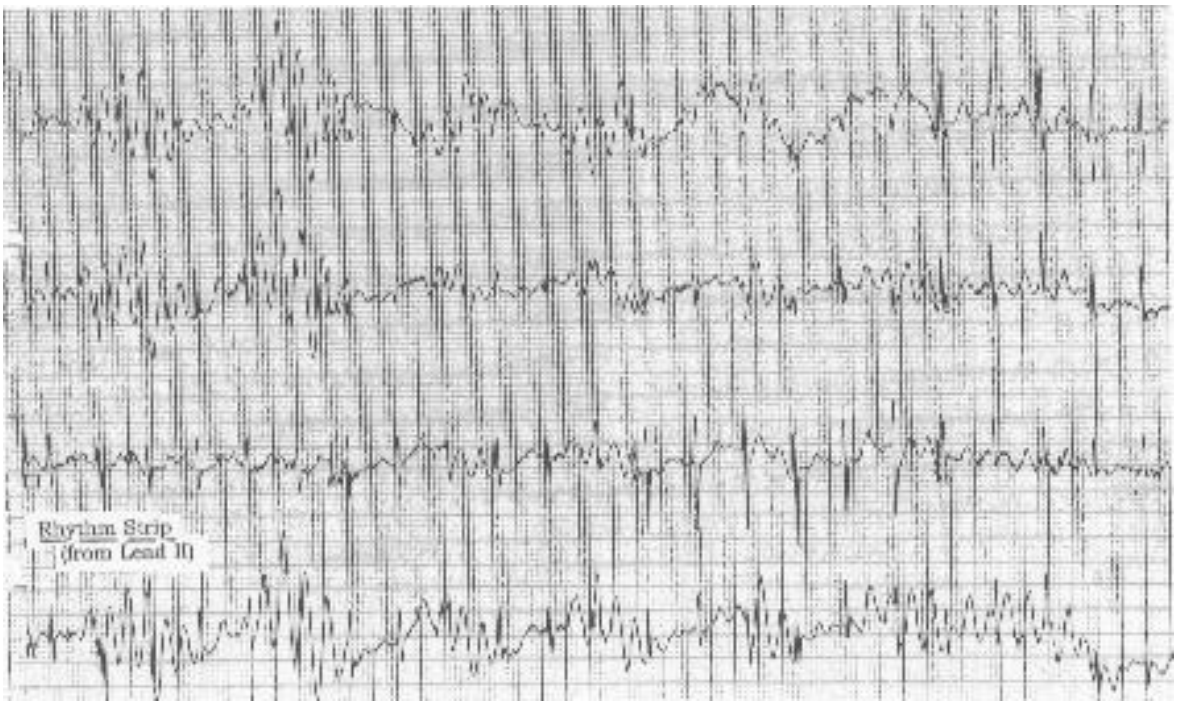

Figure. 12-lead ECG and accompanying rhythm strip recorded from an older man on multiple medications.

Clinical Scenario: The 12-lead ECG and accompanying rhythm strip shown in the Figure were obtained from an older man who presented with acute dyspnea from pneumonia. He was on multiple medications, and was in moderate-to-severe respiratory distress at the time this ECG was recorded. Is the rhythm Torsades de Pointes?

Interpretation/Answer: At first glance, the tracing in the lead II rhythm strip clearly resembles Torsades, as there appears to be an intermittently large amplitude sinusoidal pattern with alternating polarity. However, this is not what is happening. The clue to the true etiology of the rhythm lies with careful surveillance of all leads on the 12-lead ECG. This reveals an underlying regular supraventricular (narrow QRS complex) tachycardia that is best seen in leads III, V_3, V_4, and V_5. The relatively small baseline undulations in these leads are clearly identified as artifact. Armed with this knowledge, one can prove artifact as the cause of baseline distortion in the simultaneously recorded rhythm strip at the bottom of the Figure by beat-to-beat comparison with the rhythm in leads III and V_3. Doing so should make it apparent that the underlying narrow QRS rhythm continues without interruption throughout the lead II rhythm strip. This underlying rhythm is sinus tachycardia, with intermittent sinusoidal-appearing artifact produced by this patient's respiratory distress.

Recognition of artifact is often a challenging endeavor. Perhaps the two most helpful clues toward facilitating recognition are: I) Look first at the patient for correlation with the clinical setting (ie, unresponsiveness consistent with malignant arrhythmia?—or "telltale activity" such as hand tremor, performance of CPR, seizure, or respiratory distress?); and II) Look carefully for an underlying rhythm, which if present continuously throughout the tracing despite distorting activity proves artifact as the cause. ■

In Future Issues:

Short Sleep Duration and Obesity

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Britain to Allow Over-the-Counter Sales of Zocor

The British government will soon allow over-the-counter (OTC) sales of Merck's simvastatin (Zocor), marking the first time any country has allowed the OTC sale of a statin. The drug lost its patent protection in England last year, and Merck is eager to make up for some lost revenues by entering the lucrative OTC market. It is likely the drug will be available in an OTC dose of 10 mg. Pharmacists will be asked to carry out a simple screening questionnaire on the spot to screen for appropriateness and safety. Not everyone is happy about the OTC switch however. An editorial in the British journal *Lancet* stated that there is insufficient evidence to justify the OTC switch and implied that the British government is simply trying to save money by defraying prescription drugs costs. Currently over 1.8 million patients in England take statins at a cost of over $1.1 billion per year.

FDA Rejects Plan B Bid

FDA regulators have rejected a bid from Barr Pharmaceuticals to market their "morning after pill" as an OTC. The product, called Plan B, contains 0.75 mg of levonorgestrel, a progestin commonly used in birth control pills. Plan B is marketed as an emergency contraceptive that can be used up to 72 hours after unprotected intercourse or suspected contraceptive failure. The decision by the FDA was somewhat surprising as it went against the recommendation the agency's own advisers who, last December, voted overwhelmingly in favor of the over-the-counter switch for Plan B. The decision prompted some groups to suggest that political pressure from the Bush administration was responsible for the denial. The FDA, however, stated in its rejection letter that they were concerned about the safety of the product for younger women, and kept the door open by suggesting that more data may prompt a reconsideration. In the meantime, Plan B is still available by prescription.

Recombinant Erythropoietin Products May Stimulate Tumor Growth

Two recent studies have raised the question of whether recombinant erythropoietin products may stimulate tumor growth in cancer patients. One study, published in the October 2003 *Lancet*, reviewed 351 adult patients with head neck cancer who were randomized to subcutaneous erythropoietin or placebo 3 times weekly prior to radiation therapy and continuing throughout radiation therapy. Patients treated with erythropoietin had improved hemoglobin concentrations, but otherwise had poor outcomes. Median locoregional progression-free survival was 745 days with placebo and 406 days with erythropoietin (relative risk, 1.62; [95% CI, 1.22-2.14]; P = .0008). Overall,

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over the 4 years of study, 52% of placebo-treated patients died, compared to 61% of erythropoietin treated patients (RR 1.39; [95% CI, 1.05-1.82]; P = .02). A second study in Europe of erythropoietin in breast cancer patients was terminated early because patients receiving the drug had lower 12 month survival rates than patients receiving placebo (70% vs 76%; P = .0117). An editorial in the December 17th Journal of the National Cancer Institute reviewed this issue and raised the plausibility of the findings. The authors noted that erythropoietin receptors have been found on head and neck cancer cells, prostate cancer cells, and ovarian cancer cells, as well as breast, renal, and uterine cancer cells. They also noted that the preliminary data suggest that some of these cancers may proliferate in the presence of erythropoietin.

The editorial concluded by calling for more research into the possible relationship between erythropoietin and poor outcomes in the treatment of cancer patients. The FDA's Oncologic Drugs Advisory Committee recently met in May, and backed a proposal by Johnson & Johnson (makers of Procrit) and Amgen (makers of Aranesp) to study this issue. The exact design of these studies is still to be delineated, but both companies have pledged to collaborate on such research.

Rosuvastatin: Market's Most Potent Statin

Rosuvastatin (Crestor-Astra Zeneca) appears to be the most potent statin currently marketed. In a study of 3140 patients with CAD, atherosclerosis, or type 2 diabetes, patients were randomized to rosuvastatin 10 mg, atorvastatin 10 or 20 mg, simvastatin 20 mg, or pravastatin 40 mg for 8 weeks. Patients either remained on these treatments or were switched from other statins to rosuvastatin. The primary pinpoint was a LDL cholesterol of < 116 mg/dL. Significant improvement in LDL cholesterol goal achievement was found for patients who were switched to rosuvastatin 10 mg compared with patients who remained on atorvastatin 10 mg (86% vs 80%; P < 0.5), simvastatin 20 mg (86% vs 72%, P <.001), and pravastatin 40 mg (88% vs 66%, P < .0001). For patients who were switched from atorvastatin 20 mg to rosuvastatin 20 mg, the rate at goal was 90% vs 84% (P < .01) (*Am Heart J*. 2004;147:705-712). But while rosuvastatin appears to be the most potent statin, it may carry a higher dose related risk of muscle toxicity including myositis and rhabdomyolysis. Astra Zeneca has recently acknowledged 4 cases of rhabdomyolysis in patients who were taking 40 mg of rosuvastatin, and has urged physicians in England to avoid initial high dose therapy with the drug, instead starting at 10 mg and titrating with appropriate follow-up.

FDA Actions

Immunex Corp.'s etanercept (Enbrel) has been approved for use in patients older than the age of 18 with moderate-to-severe plaque psoriasis. Enbrel is currently marketed for use in patients with ankylosing spondylitis, psoriatic arthritis, moderate to severe rheumatoid arthritis, and juvenile rheumatoid arthritis. The expansion of indications to treat psoriasis was expected after 2 phases.

All studies showed improvement with treatment up to 1 year. Etanercept, which is a tumor necrosis factor inhibitor, joins the biologics alefcept (Amevive) and efalizumab (Raptiva) in the suddenly rather crowded market for the treatment of psoriasis.

The FDA has approved Indevus Pharmaceutical's trospium chloride (Sanctura), for the treatment of overactive bladder with symptoms of the urge urinary incontinence, urgency and frequency. The drug is a muscarinic receptor antagonist, and as such, has side effects that include dry mouth and constipation. It is, however, relatively well-tolerated with fewer drug-drug interactions than currently available medications.

Fondaparinux (Arixtra-Fonda BV), the synthetic selective factor Xa inhibitor, has been given the expanded indication for treatment of acute pulmonary embolism and acute deep venous thrombosis without PE when coadministered with warfarin. Previously, the drug had been approved for prevention of DVT in the setting of orthopedic surgery.

Salix Pharmaceuticals has received approval to market rifaximin (Xifaxan) for the treatment of travelers diarrhea caused by noninvasive strains of *Escherichia coli*. The drug is unique in that it is minimally absorbed (< 0.5%) after oral administration, and exerts its action only in the gut. It is not for use in patients with diarrhea associated with fever or bloody stools, or pathogens other than *E. coli*. The drug is approved for patients age 12 and older and appears to be well-tolerated. ■