(1.3-2.4) for vitamin K antagonists (such as warfarin). Combined use of these drugs significantly increased the risk of GI bleeding, to 2.3 (1.7-3.3) for dipyridamole with aspirin, 5.3 (2.9-9.5) for vitamin K antagonists with aspirin, and 7.4 (3.5-15) for clopidogrel with aspirin. During the study period, from 2000 through 2004, exposure to combined antithrombotic regimens increased by 425% in the population of 470,000 residents of Funen County, Denmark.

Some prominent medical journals have banned, for some time, the use of conclusions in articles that “more research is needed” on this subject. However, the findings in the article by Zhang et al. beg for more research.

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Rhythm Versus Safety in Amiodarone Therapy

Amiodarone (Cordarone, Pacerone) is a powerful antiarrhythmic that is effective in converting atrial fibrillation (AF) to sinus rhythm and superior to sotalol in maintaining sinus rhythm. In 665 patients who were receiving anticoagulants and had persistent AF, Singh et al. found a median time to recurrence of AF of 487 days in the amiodarone group versus 74 days in the sotalol group and 6 days in the placebo group, with improved quality of life and improved exercise performance in the amiodarone group. In this study known as the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T), spontaneous conversion occurred in 72.1% of amiodarone patients, 24.2% for sotalol, and 0.8% for placebo. However, the use of amiodarone in AF is not approved by the U.S. Food and Drug Administration (FDA). The unlabeled (off-label) uses of amiodarone include conversion of atrial fibrillation and maintenance of sinus rhythm, and treatment of supraventricular tachycardia.

Amiodarone has also been shown to be a useful antiarrhythmic in patients after cardiac surgery in the clinical trial known as PAPABEAR (Prophylactic Amiodarone for the Prevention of Arrhythmias that Begin Early After Revascularization, Valve Replacement, or Repair) in which atrial tachyarrhythmia occurred less frequently in amiodarone patients (16.2%) compared with placebo (29.5%). The overall hazard ratio (HR) for tachyarrhythmia was 0.52 (95% confidence interval [CI], 0.34-0.69), and the HR was significantly less than 1.0 for all subgroups of patients, including patients younger than 65 years, patients aged 65 years or older, patients who had coronary artery bypass graft (CABG) only, patients who had valve replacement/repair surgery with or without CABG surgery, patients who received preoperative beta-blocker therapy, and patients who did not receive preoperative beta-blocker therapy.

Assessment of the medical treatment of AF from 1991 to 2000 showed that amiodarone replaced quinidine as the dominant sinus rhythm drug by 2000. For 1,355 visits for patients with AF obtained from the National Ambulatory Medical Care Survey (NAMCS), a nationally representative assessment of office-based physician practice, overall use of drugs to control cardiac rhythm decreased from 72% of visits in 1991-1992 to 56% in 1999-2000 ($P = 0.01$ for trend) due to declining digoxin use (64% to 37%, $P <0.001$ for trend). The absolute rate of use of beta-blockers, calcium channel blockers, and sinus rhythm medication did not change over the 10 years, but amiodarone use increased from 0.2% to 6.4% ($P <0.001$ for trend) while quinidine use decreased from 5.0% to 0.0% ($P = 0.01$ for trend).

The direct cost of amiodarone is not a factor in its use today. Amiodarone was approved by the FDA on December 27, 1985, as the product Cordarone. Since it was approved more than 20 years ago, it has been available by generic name for several years. The average managed care organization price per day of therapy in 2006 is $2.00 or less.
While amiodarone is relatively cheap, it is associated with significant toxicity. In a prospective study of 403 patients with AF, Roy et al. found amiodarone reduced the recurrence of AF to 35% versus 63% for sotalol, but adverse events contributed to discontinuation of drug therapy in 18% of patients receiving amiodarone versus 11% of those treated with sotalol or propafenone. In the 2006 Guidelines for the Management of Patients with Atrial Fibrillation from the American College of Cardiology, American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology, amiodarone is positioned as alternate second-line therapy to digoxin in AF patients with heart failure, but warnings include pulmonary toxicity, skin discoloration, hypothyroidism, hyperthyroidism, corneal deposits, optic neuropathy, warfarin interaction, sinus bradycardia. Amiodarone also is classified as a Level 1 risk to cause torsades de pointes, although the likelihood is listed as “low.”

Package labeling for amiodarone lists a host of potential toxicities, several of which may be fatal. The most important toxicity in amiodarone package labeling is pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis), which occurs in as many as 10% to 17% of patients with ventricular arrhythmias at doses of about 400 mg/day, but the reported prevalence of pulmonary toxicity is 2% to 7% in most clinical trials of amiodarone. However, pulmonary toxicity secondary to amiodarone is fatal in about 10% of the cases.

Compared with pulmonary toxicity, liver injury is “common” with amiodarone, evidenced by elevated liver enzymes, but is usually mild and asymptomatic. Guidelines for the use and monitoring of amiodarone from the American Academy of Family Physicians list a prevalence of 1% for liver toxicity associated with amiodarone as measured by liver enzyme levels 3 times higher than normal. However, overt liver disease can occur with amiodarone and, while rare, can be fatal. Hypothyroidism occurs in 2% to 10% of patients who receive amiodarone, and hyperthyroidism occurs in about 2% of patients.

Other concerns include the possible development of significant heart block or sinus bradycardia in 2% to 5% of patients who receive amiodarone and possible exacerbation of arrhythmia that may make the arrhythmia less well tolerated and more difficult to reverse, also in 2% to 5% of patients. Therefore, the package label for amiodarone suggests the use of amiodarone as second-line therapy in ventricular arrhythmias, consistent with second-line status for amiodarone in the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation.

In May 2005, amiodarone was the subject of a Dear Healthcare Professional letter from the FDA warning of potentially fatal pulmonary toxicity, hepatic injury and worsened arrhythmia. The product label in 2006 includes a “black box” warning that amiodarone should be used only in patients with life-threatening ventricular arrhythmias due to substantial toxicity associated with its use. For patient safety, the product label for amiodarone recommends monitoring of liver enzymes on a “regular basis” without specific recommendations on what constitutes a “regular basis.” Thyroid function monitoring is recommended at “baseline and periodically during therapy”; “periodically” is not defined.

Raebel et al. in this issue of JMCP take a tight window of 6 months follow-up to proclaim that amiodarone patients in 10 HMOs were shortchanged in liver and thyroid function monitoring during a data capture period in 1999-2001. While the toxicities associated with the use of amiodarone have been known for some time, its use increased significantly by 1999-2000, particularly in AF patients. Certainly, the risks associated with amiodarone are more prominent today than in 1999-2001. So, judgment of clinician adherence to monitoring guidelines and protection of patient safety needs to be tempered with observation of the time period examined.

There may also be a methodological concern in the study by Raebel et al. that would suggest that the clinicians who cared for the patients in the 10 HMOs may not be guilty of under-care. In addition to the fact that the product label for amiodarone is not specific with respect to what constitutes either “regular” or “periodic” monitoring, it is possible that many patients were loaded with amiodarone as inpatients, as recommended in dose administration instructions in the product label. A total of 39% of patients in this study had 1 or more hospitalizations in the 6-month period prior to an outpatient claim for amiodarone, and 22% were hospitalized 1 or more times during the average 6-month period following the first outpatient claim for amiodarone. Since Raebel et al. did not have consistent records of inpatient laboratory tests, their reported rate of laboratory monitoring for liver function and thyroid function may be understated. Both liver function, measured by alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and thyroid function, measured by thyroid-stimulating hormone (TSH), are components of general laboratory panels.

The authors did, however, assess the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the medical claims relative to the medical record. While medical claims generally did a good to excellent job of representing the medical record, the NPV of 73% for thyroid function tests indicates that 27% of the negatives (i.e., a finding that no laboratory testing took place according to the medical claims data) were actually false-negative (i.e., testing did occur according to documentation in the medical record).

The methodology employed in the study by Raebel et al. is also associated with possible overestimation of the average exposure to amiodarone. The data reported in Table 4 of that article show that 19% of patients received 2 “dispensings” or less, and 45% of patients received 3 dispensings or less of amiodarone in the average 6-month follow-up period. Since a mail-service pharmacy option with a days supply greater than 1 month was uncommon in the 10 HMOs at the time and...
pharmacy benefits generally restricted each dispensing to a 1-month supply, it appears possible that some of the amiodarone patients did not receive amiodarone during the entire 6-month follow-up. Since the researchers did not collect days supply as part of their study design, the median and range of actual days supply of amiodarone dispensed to these patients are unknown. Discontinuation of amiodarone therapy would be cause for discontinuation of laboratory monitoring for side effects of amiodarone.

Also left unanswered in the study by Raebel et al. are questions about the safety of amiodarone in combination with other drugs. Amiodarone is metabolized by the cytochrome P3A enzyme, resulting in many potential drug-drug interactions. About 18 months after the close of the data collection period in the study by Raebel et al., the label for simvastatin (Zocor) was changed in June 2002 to include a warning specific for coincident use with amiodarone. The label change was approved by the FDA on May 6, 2002, making simvastatin the only statin available in the United States with drug interaction warning specific to amiodarone.

Monitoring patient response to therapy and threats to patient safety are important quality initiatives now and in the future. A study of the quality of amiodarone monitoring performed today would presumably include laboratory monitoring for pulmonary function, capture and reporting the number of days supply of amiodarone dispensed to more accurately estimate actual drug exposure, the dose of amiodarone dispensed per day (to more accurately estimate dose titration as well as the quantity of drug exposed to the patient), the specific indication for use of the drug in each patient, and concomitant use with drugs that are contraindicated or that otherwise have warnings regarding coincident use. Even expert practitioners can miss the drug interaction between amiodarone and simvastatin, as evidenced in an April 2003 case report involving rhabdomyolysis in a 77-year old male evaluated nearly 1 year after the addition of the specific warning to the label of simvastatin for its interaction with amiodarone. And, assessment of the adequacy of monitoring therapy with amiodarone to protect patient safety would continue for longer than 6 months, particularly since amiodarone is a drug used in high-risk patients in whom toxicity as manifest by either liver enzymes or TSH levels is quite likely secondary to patient survival, particularly in a period as short as 6 months.

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