

BY DIANA MAHONEY
New England Bureau

The adult congenital heart disease

sociation guidelines writing committee. "In particular, there are a substantial number of young adults with single-ventricle physiology, systemic right ventricles, or complex intracardiac baffles who are now entering adult life," the authors wrote in the executive summary of the guidelines, which will be published in the Dec. 2, 2008, issues of both the *Journal of the American College of Cardiology* and *Circulation* and which are available in the online editions of each issue.

In addition, certain clinical scenarios warrant consultation with, treatment at or transfer to, a regional adult CHD center. Such scenarios include hospital admission for urgent or acute care in most cases; the performance of diagnostic or interventional procedures; surgical procedures requiring general anesthesia or conscious sedation; urgent or acute care of cardiac problems; and urgent or acute

must be remembered that OxyContin Tablets cannot be crushed or divided for administration.

iatric Use

controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% (see PHARMACOKINETICS AND METABOLISM). The total number of subjects (445) in clinical studies of OxyContin, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with propionate initiation of therapy and dose titration, no untoward or unexpected side effects were seen in elderly patients who received OxyContin. Thus, the usual doses and dosing intervals are appropriate for these patients. As with all opioids, the starting dose should be reduced to 1/3 to 1/2 of the usual dosage in debilitated, non-tolerant patients. Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are used in conjunction with other agents that depress respiration.

atory Monitoring

to be the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

atic Impairment

study of OxyContin in patients with hepatic impairment indicates greater plasma concentrations in patients with normal function. The initiation of therapy at 1/3 to 1/2 the usual doses and careful surveillance is warranted.

renal Impairment

patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in patients with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical response.

nder Differences

pharmacokinetic studies, opioid-naïve females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment by weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

VERSE REACTIONS

The safety of OxyContin® was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received OxyContin in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

rious adverse reactions which may be associated with OxyContin Tablet therapy in clinical use are observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, (to an even lesser degree) circulatory depression, hypotension, or shock (see OVERDOSAGE).

non-serious adverse events seen on initiation of therapy with OxyContin are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be observed and managed as a part of opioid analgesia. The most frequent (>5%) include: constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and asthenia.

many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as tolerance to the medication is continued and some degree of tolerance is developed.

clinical trials comparing OxyContin with immediate-release oxycodone and placebo revealed a similar severe event profile between OxyContin and immediate-release oxycodone. The most common adverse events (>5%) reported by patients at least once during therapy were:

	OxyContin (n=227)	Immediate-Release (n=225)	Placebo (n=45)
	(%)	(%)	(%)
Constipation	(23)	(26)	(7)
Nausea	(23)	(27)	(11)
Somnolence	(24)	(4)	(4)
Dizziness	(13)	(16)	(9)
Pruritus	(13)	(12)	(2)
Headache	(12)	(14)	(7)
Itching	(7)	(8)	(7)
Dry Mouth	(6)	(7)	(2)
Thirst	(6)	(7)	—
Sweating	(5)	(6)	(2)

the following adverse experiences were reported in OxyContin®-treated patients with an incidence between 1% and 10%. In descending order of frequency they were: anorexia, nervousness, insomnia, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

the following adverse reactions occurred in less than 1% of patients involved in clinical trials or were reported in postmarketing experience.

ood and lymphatic system disorders: lymphadenopathy

rdiary disorders: palpitations (in the context of withdrawal)

nd and labyrinth disorders: tinnitus

ocrine disorders: syndrome of inappropriate antidiuretic hormone secretion (SIADH)

id disorders: abnormal vision

rointestinal disorders: dysphagia, eructation, flatulence, gastrointestinal disorder, ileus, decreased appetite, stomatitis

renal disorders and administration site conditions: chest pain, edema, facial edema, malaise, pain, peripheral edema, thirst, withdrawal syndrome (with and without seizures)

mus system disorders: anaphylactic or anaphylactoid reaction (symptoms of reactions and infestations: pharyngitis

ury, poisoning and procedural complications: accidental injury

estigations: hyponatremia, increased hepatic enzymes, ST depression

etabolism and nutrition disorders: dehydration

culoskeletal and connective tissue disorders: neck pain

mus system disorders: abnormal gait, anorexia, hyperkinesia, hypertonia (muscular), hypesthesia, paresthesia, migraine, paresthesia, seizures, speech disorder, stupor, syncope, taste perversion, motion, vertigo

ychiatric disorders: agitation, depersonalization, depression, emotional lability, hallucination

mal and urinary disorders: dysuria, hematuria, polyuria, urinary retention, urination impaired

roductive system and breast disorders: amenorrhea, decreased libido, impotence

roductive, thoracic and mediastinal disorders: cough increased, voice alteration

mal and subcutaneous tissue disorders: dry skin, exfoliative dermatitis, urticaria

cular disorders: vasodilation

ERDOSAGE

oxycodone usage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, hypothermia, hypotension, and death.

accidents due to overdose have been reported with abuse and misuse of OxyContin®, by ingesting, swallowing, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when OxyContin is abused concurrently with alcohol or other CNS depressants, including other opioids.

the treatment of oxycodone overdose, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require direct massage or defibrillation.

pure opioid antagonists such as naloxone or nalmefene are specific antagonists against respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. In patients who are physically dependent on any opioid agent including OxyContin, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

FETY AND HANDLING

OxyContin Tablets are solid dosage forms that contain oxycodone, which is a controlled substance. Like morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act.

OxyContin has been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information how to prevent and detect abuse or diversion of this product.

healthcare professionals can telephone Purdue Pharma's Pharmacist Services Department 888-726-7535) for information on this product.

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care of noncardiac problems in high-risk patients.

The guidelines also address the psychosocial needs of adult CHD patients with the recommendation that the comprehensive care of these patients should incorporate individual and family psychosocial screening, counseling, and education regarding the possible social, emotional, and vocational impact of the condition.

Because CHD patients are at increased risk for infectious endocarditis, it is important that patients and their families be educated about the signs and symptoms of infectious complications, as well as how to prevent them, according to the authors.

In particular, the guidelines recommend antibiotic prophylaxis in high-risk CHD patients "before dental procedures that involved manipulation of the gingi-

val tissue or the periapical region of teeth or perforation of the oral mucosa." Antibiotic prophylaxis also should be considered before vaginal delivery at the



An increasing number of patients are now surviving into adulthood with complex cardiac anatomy and physiology.

DR. WARNES

time of membrane rupture in patients with a prosthetic cardiac valve or in whom prosthetic material was used for valve repair and patients with unrepaired and palliated cyanotic CHD.

However, antibiotic prophylaxis against infectious endocarditis "is not recommended for nondental procedures [such as esophagogastroduodenoscopy or

colonoscopy] in the absence of active infection," the authors wrote in the guidelines.

Pregnancy and contraception require special consideration in women with CHD. With respect to contraception, oral estrogen-containing drugs are not recommended for patients at risk of thromboembolism, including those with pulmonary arterial hypertension or cyanosis related to an intracardiac shunt, according to the guidelines. Regarding pregnancy, patients are advised to consult with an adult CHD expert to determine a labor and delivery management plan prior to becoming pregnant.

In addition to the general recommendations for the care of adult CHD patients, the guidelines also include comprehensive information on the clinical features, diagnosis, treatment options, activity limitations, pregnancy risks, and preventive strategies related to specific lesions, such as atrial, ventricular, or

atrioventricular septal defects; patent ductus arteriosus; left-sided heart obstructive lesions; right ventricular outflow tract obstruction; pulmonary artery hypertension/Eisenmenger physiology; and tetralogy of Fallot.

The adult CHD guidelines were developed in collaboration with the American Society of Echocardiography, the Canadian Cardiovascular Society, the Heart Rhythm Society, the International Society for Adult Congenital Cardiac Disease, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons.

While the recommendations are evidence based wherever possible, "unlike other ACC/AHA practice guidelines, there is not a large body of peer-reviewed published evidence to support most recommendations," the authors wrote. For this reason, the evidence supporting many of the recommendations comes from the consensus of experts. ■

In RA Patients, Cardiovascular Risk Matches Type 2 Diabetes

BY BETSY BATES
Los Angeles Bureau

SAN FRANCISCO — Patients who have rheumatoid arthritis should be assessed annually for cardiovascular risk factors, a recommendation necessitated by a heart disease risk profile that equates to that of those with type 2 diabetes, a European task force concluded.

"Cardiovascular risk management is urgently needed for patients with rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis," said Dr. Michael T. Nurmohame, who was speaking on behalf of the European League Against Rheumatism cardiovascular disease risk management task force at the annual meeting of the American College of Rheumatology.

Task force recommendations highlighted at the meeting included:

- Characterizing of rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis as "high-risk" conditions with regard to cardiovascular disease, similar to diabetes.
- Launching annual screening for cardiovascular risk of every RA patient, with consideration of screening of ankylosing spondylitis and psoriatic arthritis patients as well.
- Providing every patient with lifestyle recommendations for lowering cardiovascular risk.
- Emphasizing aggressive control of disease activity to suppress inflammation and lower cardiovascular risk.
- Adapting cardiovascular risk scoring models (such as the newly adapted Systematic Coronary Risk Evaluation SCORE) by a factor of 1.5 to account for elevated baseline risk associated with inflammatory rheumatic diseases.
- Considering of treatment with statins and/or antihypertensive drugs according to cardiovascular management targets established by local guidelines; or, if no local guidelines exist, when targets exceed 10-year cardiovascular mortality risk models

established in the newly adapted SCORE.

► Acknowledging that the role of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory drugs is not well established in RA patients.

► Limiting corticosteroids to the lowest possible doses.

The task force consisted of 21 rheumatologists, internists, cardiologists, and epidemiologists representing nine European countries.

Its work was prompted by the increasing recognition that those patients who have rheumatoid arthritis face a steeply elevated risk in cardiovascular diseases, said Dr. Nurmohame, who is a rheumatologist at the VU University Medical Center and Jan van Breemen Institute in Amsterdam.

The risk can only be partially explained by traditional risk factors, with inflammatory processes serving as the apparent "missing link," he suggested.

Earlier this year, Dr. Nurmohame and his associates published the results of the CARRÉ study, in which they compared cardiovascular risk in 353 patients with rheumatoid arthritis with two groups of similarly aged patients who were enrolled in the population-based Hoorn cohort study: 194 of the patients had type 2 diabetes and 258 healthy controls (Ann. Rheum. Dis. 2008 Aug. 12 [doi:10.1136/ard.2008.094151]).

The prevalence of cardiovascular disease was 5% in nondiabetic patients with no rheumatoid arthritis; 12.4% in patients with type 2 diabetes; and 12.9% in patients with RA.

Some of that risk can be accounted for by increased hypertension, dyslipidemia, and lifestyle factors in the RA population, he said.

However, inflammatory rheumatic diseases themselves also seem to confer an independent risk that should be accounted for in models that predict cardiovascular mortality, Dr. Nurmohame commented. ■

Restrictions on Ranolazine's Label Lifted, Cuts HbA_{1c}

BY ELIZABETH MECHCATIE
Senior Writer

The Food and Drug Administration has approved a revised indication and several label additions for the angina drug ranolazine, including a statement that the drug reduced hemoglobin A_{1c} in people with diabetes.

The indication is still for "the treatment of chronic angina, but "the second-line restriction on the use of ranolazine to treat patients with chronic angina has been removed," according to an announcement issued by the FDA.

Previously, the indication was for treatment of chronic angina, but with the added statement that it should be reserved for patients who have not had an adequate response with other antianginal drugs, because ranolazine increases the QT interval.

The additional statement has been removed from the revised label, with the information about the QT interval prolongation now in the warnings and precaution section.

Also added to the label is a statement that cites the significantly lower rate of arrhythmias in patients with coronary heart disease who were treated with ranolazine in the MERLIN-TIMI 36 trial, compared with those on placebo, CV Therapeutics Inc. noted in its announcement of the approval.

The indications section of the revised label also says that the drug can be used with β -blockers, nitrates, calcium channel blockers, antiplatelet therapy, lipid-lowering therapy, ACE inhibitors, and angiotensin receptor blockers.

CV Therapeutics markets ranolazine in extended-release tablet form as

Ranexa, which was approved in January 2006.

Ranolazine has antianginal and anti-ischemic effects, but its exact mechanism of action is not known, according to the label.

In a statement, the company said that data from the MERLIN-TIMI 36 trial were submitted to the FDA in September 2007, as part of its supplemental ap-

Previously, ranolazine's indication was restricted to patients who had not had an adequate response with other antianginal drugs.

plication. The revised label includes the statement that in the study—which compared ranolazine to placebo in more than 6,000 patients with acute coronary syndrome—no benefit was seen on outcome measures, but that the study was "somewhat reassuring regarding proarrhythmic risks, as ventricular arrhythmias were less common on ranolazine."

The incidence of arrhythmias (ventricular tachycardia, bradycardia, supraventricular tachycardia, and new atrial fibrillation) was 80% among those treated with ranolazine, compared with 87% of those on placebo, a significant difference, according to the label. However, the label also states that the difference in arrhythmias did not result in lower mortality, or reductions in arrhythmia hospitalizations or arrhythmia symptoms.

The label notes that there were no proarrhythmic effects seen on 7-day Holter recordings in 3,162 patients with acute coronary syndrome who were treated with ranolazine.

The revised label also includes the statement that ranolazine "produces small reductions in [hemoglobin A_{1c}] in patients with diabetes, the clinical significance of which is unknown," and that the drug "should not be considered a treatment for diabetes." ■