REVIEW

P. SHEENA KHURANA, MD
Department of General Internal Medicine,
Cleveland Clinic

DAVID LITAKER, MD, MSc
Department of General Internal Medicine,
Cleveland Clinic

The dilemma of nosocomial pneumonia: What primary care physicians should know

ABSTRACT

Because nosocomial pneumonia is difficult to diagnose and the need to treat it is often urgent, particularly in patients on mechanical ventilation, therapy is often empiric. We review the pathogenesis, risk factors, microbiology, diagnosis, and treatment of this disease.

KEY POINTS

Aerobic Gram-negative organisms account for half of all cases of nosocomial pneumonia, and *Pseudomonas species* are the most common. However, *Staphylococcus aureus*, a Gram-positive organism, is nearly as common as *Pseudomonas*. One third to one half of all cases are polymicrobial.

Fever, an elevated white blood cell count, and a positive sputum culture are sensitive but not specific for nosocomial pneumonia, and chest radiography and blood cultures are neither sensitive nor specific.

Empiric antibiotic therapy can be tailored on the basis of risk factors. Examples: clindamycin or metronidazole to treat anaerobic bacteria in patients at risk of aspiration, or a dual-drug regimen with good coverage against *Pseudomonas* for critically ill patients who have already received antibiotics.

NOSOCOMIAL PNEUMONIA poses a dilemma to the physician because the signs, symptoms, and diagnostic tests are often unreliable.

The dilemma: To treat empirically with broad-spectrum antibiotics, without knowing with certainty the causative organism or indeed whether the patient has pneumonia at all? To do so may save the patient's life—or may expose him or her to useless treatment and promote superinfection and emergence of antibiotic-resistant organisms. The alternative is to hold out for a definitive diagnosis. This approach may be more precise, but it may delay needed treatment or expose the patient to an invasive test (bronchoscopy) without providing a definitive answer.

INCIDENCE AND IMPACT

Nosocomial pneumonia—an infection of the lung parenchyma that is neither present nor incubating at the time of a patient's admission to the hospital[1]—is the second most common type of hospital-acquired infection in the United States (after urinary tract infections).[2] The incidence has been reported as 0.4% to 1.1% but may be as high as 25% in some intensive care units.[3]

The cost to society is great. The mortality rate ranges from 20% to 50%, the highest of the nosocomial infections.[1,2] Moreover, patients with nosocomial pneumonia spend 6 to 13 additional days in the hospital, suffer additional sickness, and accrue several billion dollars of excess health care costs each year.[4]

Factors that promote pneumonia in intubated patients

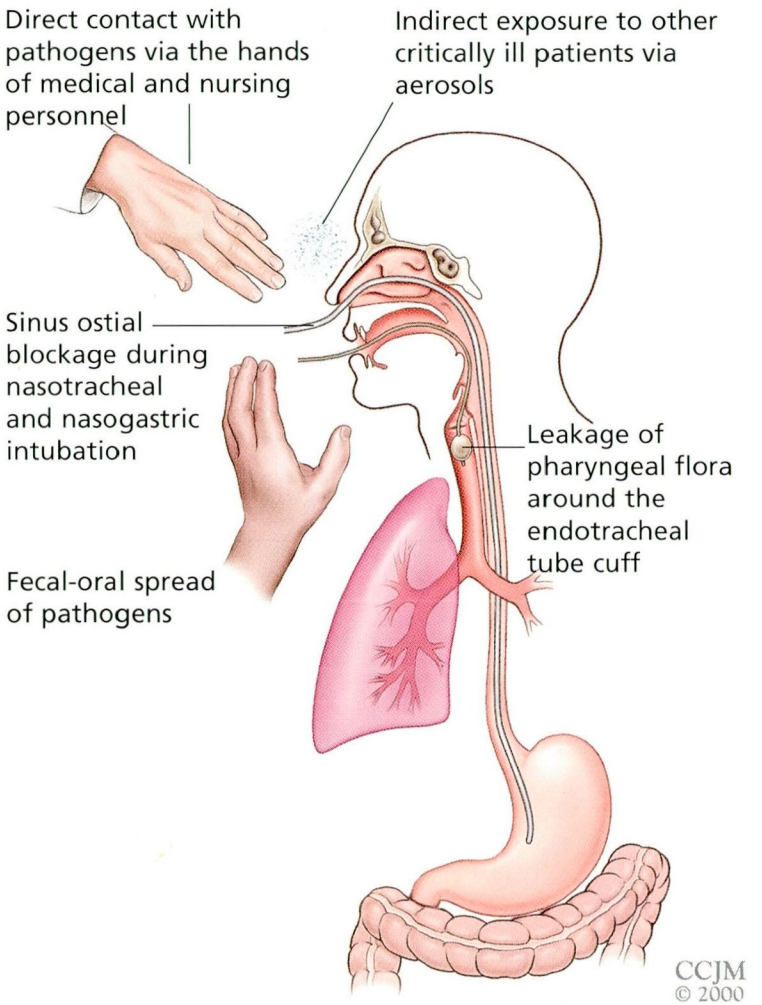


FIGURE 1

PATHOGENESIS OF NOSOCOMIAL PNEUMONIA

Colonization of the upper respiratory and gastrointestinal tracts and aspiration play key roles in the pathogenesis of nosocomial pneumonia (FIGURE 1).

Colonization of the upper respiratory tract

The normal oropharyngeal flora consists of *Streptococcus pneumoniae*, *Streptococcus* species, *Hemophilus* species, *Neisseria* species, and anaerobic bacteria. Among smokers, *Moraxella catarrhalis* is also prevalent. Gram-negative bacilli, the cause of most cases of nosocomial pneumonia, are rarely present in the oropharynx because the immune system normally resists colonization and can overcome most microbial challenges.[5]

However, gram-negative bacilli rapidly colonize the respiratory tract of ill hospitalized patients, taking advantage of changes in the epithelial cells, such as decreased mucociliary clearance or reduced ciliary action. These changes correlate with the severity of illness. As many as 75% of hospitalized patients become colonized with Gram-negative bacilli within 48 hours of admission.[2]

These organisms, particularly *Pseudomonas* species, have a predilection for the respiratory epithelium. Two features help these organisms adhere to the epithelium: pili on their external cell membranes and the ability to express protease, which destroys fibronectin in epithelial secretions.

Colonization of the gastrointestinal tract

Some organisms that colonize the upper respiratory tract come from the gastrointestinal tract. These can subsequently be aspirated and contribute to pneumonitis.[6]

The upper gastrointestinal tract is normally sterile, as most bacteria cannot survive in the acidic environment of the stomach. However, drugs that raise the gastric pH, such as those used in preventing stress ulcers in patients on ventilators, may allow Gram-negative bacilli to proliferate in the stomach.[7]

Sucralfate. An exception is sucralfate, which does not significantly alter the gastric pH. Recent randomized, controlled trials and meta-analyses[7,8] demonstrated that sucralfate use led to a lower incidence of pneumonia than did antacids or histamine$_2$-receptor blockers. Prod'hom et al[7] reported an incidence of nosocomial pneumonia of 6%, in patients receiving sucralfate, compared with 16% in those receiving antacids and 21% in those receiving H_2-receptor antagonists. Whether this benefit is due to a lesser increase in pH or to intrinsic antibacterial activity is not known. On the other hand, Simms et al[9] reported that the incidence of pneumonia was no lower with sucralfate than with cimetidine or antacids, and questioned whether stress ulcer drugs that increase the gastric pH in fact

lead to a higher incidence of pneumonia. The issue remains controversial.

Aspiration

Aspiration is often clinically occult. In one report,[2] 45% of normal subjects were observed to aspirate during sleep, as were 70% of patients with depressed consciousness. In healthy persons, the structural barriers of the lower respiratory tract and immune defenses usually prevent bacterial proliferation.

Other routes of infection

Less-common routes of infection include inhalation of infected aerosols; hematogenous spread from urinary tract infections, wounds, or catheters; and infection via contaminated hospital equipment, water sources, and hands of medical personnel.

RISK FACTORS FOR NOSOCOMIAL PNEUMONIA

Mechanical ventilation and intubation

Nosocomial pneumonia poses a major threat to patients on mechanical ventilation. As many as 25% of patients on ventilators contract pneumonia, and the risk is high even with short-term intubation for surgery.[10]

Up to 25% of respirator patients develop pneumonia

Ventilator-associated pneumonia typically imposes an increased mortality rate, in part because patients are often severely ill to begin with and have underlying lung disease, malnutrition, or other comorbid conditions.[11]

Several factors promote tracheal colonization in intubated patients:

- Leakage of pharyngeal flora around the endotracheal tube cuff
- Sinus ostial blockage during nasotracheal intubation
- Local trauma
- Reduced clearance from the lower respiratory tract
- Frequent use of other invasive devices such as suction catheters and bronchoscopes
- Indirect exposure to other critically ill patients via aerosols
- Direct contact with pathogens spread by the hands of medical and nursing personnel.

Pulmonary effects of surgery

Both anesthesia and surgery can have profound effects on ventilation and oxygenation. These changes can lead to either atelectasis or hypoxemia in the perioperative period and, in combination with the risks associated with intubation, may result in a higher incidence of nosocomial pneumonia.

From 9% to 90% of surgical patients suffer some type of postoperative pulmonary complication, depending on the definition used.[12,13] Pneumonia accounts for about a third of these complications. It results in increased morbidity and mortality and may lead to increased health care costs and hospital length of stay.[14,15] In one study in surgical patients with cancer,[16] the mean cost of caring for a patient with a postoperative infection (pneumonia, urinary tract infection, or wound infection) was $42,651, compared with $18,064 for patients without an infection.

To prevent postoperative atelectasis and pneumonia, one must identify any risk factors early.[3,17,18]

Endogenous risk factors, ie, those related to the patient, include:

- Age greater than 60 years
- Impaired preoperative cognitive function
- Chronic obstructive pulmonary disease
- Macroaspiration
- Smoking within the past 8 weeks
- Immunosuppression due to HIV infection, cancer, drugs, organ transplantation, or neutropenia
- Body mass index greater than 27.

Exogenous risk factors, ie, those related to the patient's care, include:

- Mechanical ventilation
- A thoracoabdominal incision
- Long-term intubation
- Reintubation
- Frequent ventilator circuit changes
- Tracheostomy
- Use of a nasogastric tube or enteral nutrition
- Use of histamine$_2$-receptor antagonists and antacids
- Previous antibiotic use
- Contaminated water supply or hospital equipment, inadequate handwashing.

One may be able to reduce the risk of postoperative pneumonia by having the patient stop smoking at least 8 weeks before surgery[19] and perform lung-expansion exercises such as incentive spirometry[20] and by nursing measures to prevent aspiration.[21] The role of selective prophylactic decontamination of the digestive tract with antibiotics before surgery is still controversial.

MICROBIOLOGY OF NOSOCOMIAL PNEUMONIA

Gram-negative bacteria cause more than 50% of cases of nosocomial pneumonia (TABLE 1). Polymicrobial infections may be present in 30% to 50% of all cases.[22,23]

Some organisms are more likely in certain groups of patients, such as:

- *S pneumoniae* and *H influenza* in nonintubated patients not receiving antibiotics
- *Pseudomonas*, *Acinetobacter*, and methicillin-resistant *Staphylococcus aureus* in patients who previously received antibiotics[24]
- *P aeruginosa* in patients with chronic obstructive pulmonary disease, structural lung disease, tracheostomy, or prolonged intubation, or in patients using corticosteroids.[25]
- *S aureus* in patients with diabetes or a recent history of influenza.

TABLE 1

Prevalence of causative organisms in nosocomial pneumonia

ORGANISM	PREVALENCE
Gram-negative bacteria	**52%**
Pseudomonas species	17%
Enterobacteriaceae species	11%
Klebsiella species	7%
Escherichia coli	6%
Hemophilus influenza	6%
Serratia marcescens	5%
Gram-positive bacteria	**16%**
Staphylococcus aureus	16%
Other organisms	**32%**
Proteus species	
Acinetobacter species	
Streptococcus pneumoniae	
Anaerobes	
Legionella	
Viruses	
Respiratory syncytial virus	
Adenoviruses	
Influenza	
Fungi	
Candida	
Aspergillus	

ADAPTED FROM CENTERS FOR DISEASE CONTROL AND PREVENTION. GUIDELINE FOR PREVENTION OF NOSOCOMIAL PNEUMONIA. RESPIR CARE 1994; 39:1149–1153

30% to 50% of cases are polymicrobial

Other organisms that cause nosocomial pneumonia

Less-common organisms responsible for nosocomial pneumonia range from specific bacteria to viruses and fungi.

Anaerobes rarely cause nosocomial pneumonia except in patients with aspiration.[22,26]

Legionella has caused considerable concern because it has been linked to water sources and ice machines in hospitals.[27]

Fungi such as *Aspergillus* species or *Candida albicans* can cause nosocomial pneumonia, although true candidal pneumonia is extremely rare. Isolation of *Candida* species, even from bronchoscopic samples in patients who are not neutropenic, is unlikely to be due to invasive candidiasis. Initiation of antifungal therapy in these patients is usually based on histological evidence or isolation from sterilely obtained specimens.[28] A cautious approach to treatment of fungal pneumonia is warranted because of increasing concern about the emergence of imidazole-resistant yeasts such as *Torulopsis glabrata*.[29]

Among viral causes, influenza and respiratory syncytial virus are the most common and are usually seen in community epidemics[30] and in organ transplant recipients.[31]

DIAGNOSIS OF NOSOCOMIAL PNEUMONIA

The diagnosis of nosocomial pneumonia may be difficult, as the signs and symptoms of an underlying illness may dominate the clinical

*Fleischmann R, Iwan T, Kaiko R, et al. Chronic low back pain (LBP) treatment with controlled–release (CR) and immediate–release (IR) oxycodone. Presented at the IASP; August, 1996; Vancouver, British Columbia, Canada.

OxyContin®

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

10 mg 20 mg 40 mg 80 mg

80 mg For use in opioid tolerant patients only.

Brief Summary on OxyContin® (oxycodone hydrochloride controlled-release) Tablets. Before prescribing, see complete prescribing information, including DOSAGE AND ADMINISTRATION

INDICATIONS AND USAGE:

For the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days.

CONTRAINDICATIONS:

OxyContin® is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression *(in unmonitored settings or the absence of resuscitative equipment)*, and patients with acute or severe bronchial asthma or hypercarbia. OxyContin is contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS:

OxyContin® TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OxyContin *TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY* TOXIC DOSE OF OXYCODONE.

Respiratory Depression

Respiratory depression, the chief hazard from all opioid agonist preparations, occurs most frequently in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with *significant* chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression. In such patients, *even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of* apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Head Injury

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the *presence of head injury, intracranial lesions, or other sources of preexisting increased* intracranial pressure. Oxycodone produces effects which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Hypotensive Effect

OxyContin®, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after *concurrent administration with drugs such as phenothiazines or other agents which compromise* vasomotor tone. OxyContin may produce orthostatic hypotension in ambulatory patients. OxyContin, like all opioid analgesics, should be administered with caution to patients in circulatory shock, *since vasodilation produced by the drug may further reduce cardiac output* and blood pressure.

PRECAUTIONS:

Special precautions regarding OxyContin® 80 mg Tablets

OxyContin® 80 mg Tablets are for use only in opioid tolerant patients requiring daily *oxycodone equivalent dosages of 160 mg or more. Care should be taken in the prescription of this tablet strength.* Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such *inappropriate use may have severe medical consequences.*

General — OxyContin® tablets are intended for use in patients who require oral pain therapy with an opioid agonist of more than a few days duration. As with any opioid analgesic, it is critical to adjust the dosing regimen individually for each patient.

Selection of patients for treatment with OxyContin should be governed by the same principles that apply to the use of similar controlled-release opioid analgesics. Opioid analgesics given on a fixed-dosage schedule have a narrow therapeutic index in certain patient populations, especially when combined with other drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension. Physicians should individualize treatment in every case, using non-opioid analgesics, prn opioids and/or combination products, and chronic opioid therapy with drugs such as OxyContin in a progressive plan of pain management such as outlined by the World Health Organization, the Agency for Health Care Policy and Research, and the American Pain Society.

Use of OxyContin is associated with increased potential risks and should be used only with *caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g.,* Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic *hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function;* and toxic psychosis.

The administration of oxycodone, like all opioid analgesics, may obscure the diagnosis or *clinical course in patients with acute abdominal conditions. Oxycodone may aggravate* convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Interactions with other CNS Depressants

OxyContin, like all opioid analgesics, should be used with caution and started in a reduced dosage (1/3 to 1/2 of the usual dosage) in patients who are concurrently receiving other *central nervous system depressants including sedatives or hypnotics, general anesthetics,* phenothiazines, other tranquilizers and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation or coma may result if these drugs are taken in *combination with the usual doses of OxyContin.*

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol and buprenor*phine) should be administered with caution to a patient who has received or is receiving* a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

Ambulatory Surgery

OxyContin is not recommended pre-operatively (preemptive analgesia) or for the manage*ment of pain in the immediate post-operative period (the first 12 to 24 hours following* surgery) for patients not previously taking the drug, because its safety in this setting has not been established.

Patients who are already receiving OxyContin tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given and the temporary changes in physiology caused by the surgical intervention (see PRECAUTIONS: Drug-Drug Interactions).

Post-Operative Use

Morphine and other opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

Use in Pancreatic/Biliary Tract Disease

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is the occurrence of withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

Significant tolerance should not occur in most of the patients treated with the lowest doses of oxycodone. It should be expected, however, that a fraction of cancer patients will develop some degree of tolerance and require progressively higher dosages of OxyContin to maintain pain control during chronic treatment. *Regardless of whether this occurs as a result of* increased pain secondary to disease progression or pharmacological tolerance, dosages can usually be increased safely by adjusting the patient's dose to maintain an acceptable balance *between pain relief and side effects. The dosage should be selected according to the patient's* individual analgesic response and ability to tolerate side effects. Tolerance to the analgesic effect of opioids is usually paralleled by tolerance to side effects, except for constipation.

Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug or may be precipitated through the administration of drugs with opioid antagonist activity (see OVERDOSAGE). If OxyContin is abruptly discontinued in a physically dependent *patient, an abstinence syndrome may occur.* This is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate or heart rate.

If signs and symptoms of withdrawal occur, patients should be treated by reinstitution of opioid therapy followed by a gradual, tapered dose reduction of OxyContin combined with symptomatic support.

Information for Patients/Caregivers

If clinically advisable, patients receiving OxyContin should be given the following information by the physician:

1. OxyContin tablets were designed to work properly only if swallowed whole. They may release all their contents at once if broken, chewed or crushed, resulting in a risk of overdose.
2. Report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
3. Do not adjust the dose of OxyContin without consulting the prescribing professional.
4. OxyContin may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
5. Do not combine OxyContin with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because additive effects may occur.
6. Women of childbearing potential who become, or are planning to become, pregnant should consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
7. OxyContin is a potential drug of abuse. Patients should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
8. Patients may pass empty matrix "ghosts" (tablets) via colostomy or in the stool; this is of no concern since the active medication has already been absorbed.
9. If patients have been receiving treatment with OxyContin for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the OxyContin dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.

Laboratory Monitoring

Due to 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.

Interactions with Alcohol and Drugs of Abuse

Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids or illicit drugs which cause central nervous system depression.

Use in Drug and Alcohol Addiction

OxyContin is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug-Drug Interactions

Opioid analgesics, including OxyContin, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Oxycodone is metabolized in part to oxymorphone via CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs and antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

Use with CNS Depressants

OxyContin, like all opioid analgesics, should be started at 1/3 to 1/2 of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers and alcohol because respiratory depression, hypotension and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

Mutagenicity/Carcinogenicity

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. Coli test with and without metabolic activation at doses of up to 5000 µg, chromosomal aberration test in human lymphocytes (in the absence of metabolic activation and with activation after 48 hours of exposure) at doses of up to 1500 µg/ml, and in the in vivo bone marrow micronucleus assay in mice (at plasma levels of up to 48 µg/ml). Mutagenic results occurred in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 µg/ml) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 µg/ml or greater with metabolic activation and at 400 µg/ml or greater without metabolic activation. The data from these tests indicate that the genotoxic risk to humans may be considered low.

Studies of oxycodone in animals to evaluate its carcinogenic potential have not been conducted owing to the length of clinical experience with the drug substance.

Pregnancy

Teratogenic Effects — Category B: Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg (48 mg/m²) and 125 mg/kg (1375 mg/m²), respectively. These doses are 4 and 60 times a human dose of 120 mg/day (74 mg/m²), based on mg/kg of a 60 kg adult (0.7 and 19 times this human dose based upon mg/m²). The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects — Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

Labor and Delivery

OxyContin is not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn.

Nursing Mothers

Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving OxyContin since oxycodone may be excreted in the milk. *Pediatric Use*

Safety and effectiveness in pediatric patients below the age of 18 have not been established with this dosage form of oxycodone. However, oxycodone has been used extensively in the pediatric population in other dosage forms, as have the excipients used in this formulation. *No specific increased risk is expected from the use of this form of oxycodone in pediatric patients* old enough to safely take tablets if dosing is adjusted for the patient's weight. **It must be remembered that OxyContin tablets cannot be crushed or divided for administration.**

Geriatric Use

In 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%. In clinical trials with appro*priate initiation of therapy and dose titration, no untoward or unexpected side effects were seen based on age, and the usual doses and dosing intervals are appropriate for the geriatric patient.

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.

Hepatic Impairment

*A study of OxyContin in patients with hepatic impairment indicates greater plasma concen*trations than those with normal function. The initiation of therapy at 1/3 to 1/2 the usual doses and careful dose titration is warranted.

Renal Impairment

In 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 subjects with normal renal function. Dose initiation should follow a conserva*tive approach. Dosages should be adjusted according to the clinical situation.

Gender Differences

In pharmacokinetic studies, opioid-naive females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body 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.

Rectal Administration

OxyContin Tablets are not recommended for administration per rectum. A study in normal volunteers showed a significantly greater AUC and higher C_{max} during this route of administration.

ADVERSE REACTIONS:

Serious adverse reactions which may be associated with OxyContin® tablet therapy in clinical use are those observed with other opioid analgesics, including: respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension or shock (see OVERDOSE).

The 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 expected 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.

In 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 OxyContin therapy is continued and some degree of tolerance is developed.

In clinical trials comparing OxyContin with immediate-release oxycodone and placebo, the most common adverse events (>5%) reported by patients (pts) at least once during therapy were:

	OxyContin (n=227) # Pts (%)		Immediate-Release (n=225) # Pts (%)		Placebo (n=45) # Pts (%)	
Constipation	52	(23)	58	(26)	3	(7)
Nausea	52	(23)	60	(27)	5	(11)
Somnolence	52	(23)	55	(24)	2	(4)
Dizziness	29	(13)	35	(16)	4	(9)
Pruritus	29	(13)	28	(12)	1	(2)
Vomiting	27	(12)	31	(14)	3	(7)
Headache	17	(7)	19	(8)	3	(7)
Dry Mouth	13	(6)	15	(7)	1	(2)
Asthenia	13	(6)	16	(7)	—	—
Sweating	12	(5)	13	(6)	1	(2)

The following adverse experiences were reported in OxyContin treated patients with an *incidence between 1% and 5%. In descending order of frequency they were anorexia,* nervousness, insomnia, fever, 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:

General: accidental injury, chest pain, facial edema, malaise, neck pain, pain

Cardiovascular: migraine, syncope, vasodilation, ST depression

Digestive: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, nausea and vomiting, stomatitis, ileus

Hemic and Lymphatic: lymphadenopathy

Metabolic and Nutritional: dehydration, edema, hyponatremia, peripheral edema, syndrome of inappropriate antidiuretic hormone secretion, thirst

Nervous: abnormal gait, agitation, amnesia, depersonalization, depression, emotional lability, hallucination, hyperkinesia, hypesthesia, hypotonia, malaise, paresthesia, seizures, speech disorder, stupor, tinnitus, tremor, vertigo, withdrawal syndrome with or without seizures

Respiratory: cough increased, pharyngitis, voice alteration

Skin: dry skin, exfoliative dermatitis, urticaria

Special Senses: abnormal vision, taste perversion

Urogenital: dysuria, hematuria, impotence, polyuria, urinary retention, urination impaired

DRUG ABUSE AND DEPENDENCE (Addiction):

OxyContin® is a mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone products are common targets for both drug abusers and drug addicts. Delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug.

Drug addiction (drug dependence, psychological dependence) is characterized by a preoccupation with the procurement, hoarding, and abuse of drugs for non-medicinal purposes. Drug dependence is treatable, utilizing a multi-disciplinary approach, but relapse is common. Iatrogenic "addiction" to opioids legitimately used in the management of pain is very rare.

OxyContin consists of a dual-polymer matrix, intended for oral use only. Parenteral venous injection of the tablet constituents, especially talc, can be expected to result in local tissue necrosis and pulmonary granulomas.

OVERDOSAGE:

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

In the treatment of oxycodone overdosage, 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 man*agement of circulatory shock and pulmonary edema accompanying overdose as indicated.* Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes 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. They should be administered cautiously to persons who are known, *or suspected to be, physically dependent on any opioid agonist including OxyContin®.* In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the 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.

SAFETY AND HANDLING:

OxyContin® tablets are solid dosage forms that pose no known health risk to health-care providers beyond that of any controlled substance. As with all such drugs, care should be taken to prevent diversion or abuse by proper handling.

CAUTION: DEA Order Form Required.

R_x Only.

Manufactured by The PF Laboratories, Inc., Totowa, N.J. 07512

Distributed by Purdue Pharma L.P., Norwalk, CT 06850-3590

U.S. Patent Numbers 4,861,598; 4,970,075; 5,266,331; 5,508,042; 5,549,912; and 5,656,295.

June 15, 1998 G4909-BS

TABLE 2

Value of clinical and laboratory features in diagnosing ventilator-associated pneumonia

FEATURE	SENSITIVITY (%)	SPECIFICITY (%)	POSITIVE PREDICTIVE VALUE (%)	NEGATIVE PREDICTIVE VALUE (%)
Body temperature > 38.3°C	100	25	63	100
White blood cell count < 5 or > 10 × 10^9/L	100	25	63	100
Suspected pathogens identified by sputum culture	86	30	63	60
Asymmetric infiltrate on chest radiograph	57	70	73	54

ADAPTED FROM ANDREWS CP, COALSON JJ, SMITH JD, JOHANSON WG JR. DIAGNOSIS OF NOSOCOMIAL PNEUMONIA IN ACUTE, DIFFUSE LUNG INJURY. CHEST 1981; 80:254–258, WITH PERMISSION

picture. Therefore, a good deal of suspicion is essential.

In a previously healthy person free of lung disease, clinical signs such as fever, sputum production, leukocytosis, and new asymmetric infiltrates on a chest radiograph almost invariably indicate pneumonia. Yet, in an ill, hospitalized patient, the presence or absence of these signs is often inadequate to confirm or rule out the diagnosis (TABLE 2). In a study by Fagon et al,[11] the diagnostic accuracy of clinical criteria used alone was only 77%, while regimens based on noninvasive testing alone were inappropriate in more than two thirds of cases.

Sputum analysis

The usefulness of sputum analysis depends on the quality of the specimen: contaminated specimens provide very little useful data. An acceptable sputum specimen contains fewer than 10 epithelial cells and more than 25 white blood cells per high-power field.

Limitations. Current methods of sputum analysis lack specificity. An abnormal Gram stain correlates poorly with the presence or absence of infection. In addition, sputum culture has a high false-positive rate (45%) and a less than 50% correlation with a positive blood culture.[32,33] Sputum obtained by endotracheal aspiration has a lower false-positive rate than does expectorated sputum; however, even sampling by this method may not represent lower airway flora.

Quantitative cultures of endotracheal aspirates may reduce the rate of false-positive results and compare well with cultures obtained by invasive sampling methods.[34] The diagnostic threshold is 10^5 or 10^6 colony-forming units/mL.

Elastin fiber analysis. Elastin fibers in the sputum represent necrosis of lung tissue, which can be due to a necrotizing lung infection.[35] Although this test is inexpensive, quick, and easy, it can be falsely negative in Gram-positive pneumonia[33] and falsely positive in patients with adult respiratory distress syndrome.[36] Consequently, it has not been widely accepted by physicians who commonly treat critically ill patients.

Antibody-coated bacteria detection. Tests that detect antibodies on the surface of bacteria and distinguish colonizers from true pathogens may be useful, when available, in patients with ambiguous clinical findings. In practice, however, the sensitivity and specificity of such tests have been inconsistent, limiting their applicability at present.[37,38]

Sputum cultures have a high false-positive rate

Blood cultures

Blood cultures, considered the gold standard in diagnosing many infectious diseases, have a

TABLE 3

Value of different sampling techniques in diagnosing ventilator-associated pneumonia

TECHNIQUE	SENSITIVITY (%)	SPECIFICITY (%)	POSITIVE PREDICTIVE VALUE (%)	NEGATIVE PREDICTIVE (%)
Protected brush biopsy, $\geq 10^3$ cfu/mL	42	95	83	73
Bronchoalveolar lavage, $\geq 10^4$ cfu/mL	58	95	88	79
Blind bronchial sampling, $\geq 10^4$ cfu/mL	83	80	71	89

DATA FROM PAPAZIAN L, THOMAS P, GARBE L, ET AL. BRONCHOSCOPIC OR BLIND SAMPLING TECHNIQUES FOR THE DIAGNOSIS OF VENTILATOR-ASSOCIATED PNEUMONIA. AM J RESP CRIT CARE MED 1995; 152:1982–1991.

diagnostic yield of only 11% in nosocomial pneumonia.[39] In addition, positive culture results must be interpreted cautiously in patients with suspected nosocomial pneumonia, owing to the possibility of concomitant infections associated with indwelling intravascular lines, urinary catheters, or surgical or acquired wounds.

Many conditions cause radiographic infiltrates

Radiographic evaluation

Patients who are bedridden or on a mechanical ventilator are apt to develop other pulmonary processes that may resemble pneumonia radiographically. The differential diagnosis for radiographic infiltrates includes chemical aspiration, atelectasis, adult respiratory distress syndrome, hemorrhage, and edema. Generally, only a third of hospitalized patients with an asymmetrical infiltrate on chest radiography have pneumonia histologically.[40] Moreover, the use of clinical information as an adjunct may not significantly enhance the diagnostic accuracy.[41]

In addition, a number of technical problems can limit the usefulness of chest radiography: inadequate positioning, hypoventilation, over-penetration or under-penetration of radiographic films, and overlying devices. These problems are most common in critically ill patients, who are at the greatest risk for nosocomial pneumonia.

Airway sampling techniques

Invasive lower airway sampling techniques help minimize contamination and help ensure targeted antimicrobial therapy. To reduce contamination of lower airway aspirates by upper airway secretions, protected bronchoscopic methods have been developed.

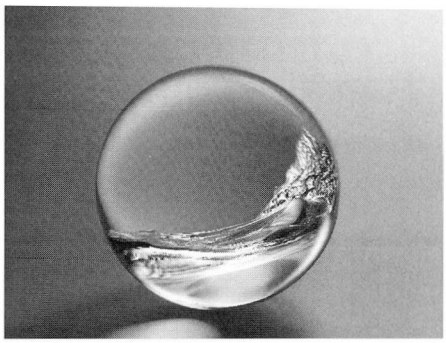
Protected brush biopsy uses a special double-catheter brush system with a distal occluding plug to reduce contamination.[36] This method is excellent in cases in which no prior antibiotics have been given.[42]

Bronchoalveolar lavage involves instilling and aspirating 100 to 120 mL of a physiologic solution such as normal saline. This method can recover many more organisms than a brush biopsy can, as it draws a sample from up to 1 million alveoli at a time. This means that the fluid can be analyzed immediately, whereas samples obtained by protected brush biopsy may have to be cultured for 48 hours.[36] In addition, previous antibiotic use does not affect the results as much as with techniques requiring active microbial growth.[42]

The diagnostic accuracy of either method may be further enhanced by using quantitative cultures. The cutoff is 10^4 colony-forming units/mL for specimens obtained through bronchoalveolar lavage and 10^3 colony-forming units/mL by protected brush biopsy. In addition, direct examination of specimens for bacteria and neutrophils may also increase the specificity of cultures obtained using these approaches. The value of these methods, however, may

Once-a-day DITROPAN® XL (oxybutynin chloride) Extended-release tablets 5, 10, 15 mg

Delivers a difference



BRIEF SUMMARY: Please see full prescribing information.

INDICATIONS AND USAGE

DITROPAN® XL is a once-daily controlled-release tablet indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

CONTRAINDICATIONS

DITROPAN® XL is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

DITROPAN® XL is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

PRECAUTIONS

General

DITROPAN® XL should be used with caution in patients with hepatic or renal impairment.

Urinary Retention:

DITROPAN® XL should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention (see **CONTRAINDICATIONS**).

Gastrointestinal Disorders:

DITROPAN® XL should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see **CONTRAINDICATIONS**).

DITROPAN® XL, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis, intestinal atony, and myasthenia gravis.

DITROPAN® XL should be used with caution in patients who have gastroesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis.

As with any other nondeformable material, caution should be used when administering DITROPAN® XL to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs in nondeformable controlled-release formulations.

Information for Patients

Patients should be informed that heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as oxybutynin chloride are administered in the presence of high environmental temperature.

Because anticholinergic agents such as oxybutynin may produce drowsiness (somnolence) or blurred vision, patients should be advised to exercise caution.

Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin.

Patients should be informed that DITROPAN® XL should be swallowed whole with the aid of liquids. Patients should not chew, divide, or crush tablets. The medication is contained within a non-absorbable shell designed to release the drug at a controlled rate. The tablet shell is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

Drug Interactions

The concomitant use of oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility.

Pharmacokinetic studies with patients concomitantly receiving cytochrome P450 enzyme inhibitors, such as antimycotic agents (e.g. ketoconazole, itraconazole, and miconazole) or macrolide antibiotics (e.g. erythromycin and clarithromycin), have not been performed.

No specific drug-drug interaction studies have been performed with DITROPAN® XL.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-month study in rats at dosages of oxybutynin chloride of 20, 80 and 160 mg/kg/day showed no evidence of carcinogenicity. These doses are approximately 6, 25 and 50 times the maximum human exposure, based on surface area.

Oxybutynin chloride showed no increase of mutagenic activity when tested in Schizosaccharomyces pompholiciformis, Saccharomyces cerevisiae, and Salmonella typhimurium test systems.

Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility.

Pregnancy: Teratogenic Effects

Pregnancy Category B

Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility or harm to the animal fetus. The safety of DITROPAN® XL administration to women who are or who may become pregnant has not been established. Therefore, DITROPAN® XL should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

Nursing Mothers

It is not known whether oxybutynin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DITROPAN® XL is administered to a nursing woman.

Pediatric Use

The safety and efficacy of DITROPAN® XL in pediatric patients have not been established.

Geriatric Use

The rate and severity of anticholinergic effects reported by patients less than 65 years old and those 65 years and older were similar (See **CLINICAL PHARMACOLOGY, Pharmacokinetics**, **Special Populations:** Gender).

ADVERSE REACTIONS

Adverse Events with DITROPAN® XL

The safety and efficacy of DITROPAN® XL was evaluated in a total of 580 participants who received DITROPAN® XL in clinical trials (429 patients, 151 healthy volunteers). These participants were treated with 5-30 mg/day for up to 4.5 months. Safety information is provided for 429 patients from three controlled clinical studies and one open label study (Table 1). The adverse events are reported regardless of causality.

Table 1: Incidence (%) of Adverse Events Reported by ≥5% of Patients Using DITROPAN® XL (5-30 mg/day)

Body System	Adverse Event	DITROPAN® XL 5-30 mg/day (n=429)
General	headache	9.8
	asthenia	6.8
	pain	6.8
Digestive	dry mouth	60.8
	constipation	13.1
	diarrhea	9.1
	nausea	8.9
	dyspepsia	6.8
Nervous	somnolence	11.9
	dizziness	6.3
Respiratory	rhinitis	5.6
Special senses	blurred vision	7.7
	dry eyes	6.1
Urogenital	urinary tract infection	5.1

The most common adverse events reported by patients receiving 5-30 mg/day DITROPAN® XL were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related.

The discontinuation rate for all adverse events was 6.8%. The most frequent adverse event causing early discontinuation of study medication was nausea (1.9%), while discontinuation due to dry mouth was 1.2%.

In addition, the following adverse events were reported by 2 to <5% of patients using DITROPAN® XL (5-30 mg/day) in all studies. **General:** abdominal pain, dry nasal and sinus mucous membranes, accidental injury, back pain, flu syndrome; **Cardiovascular:** hypertension, palpitation, vasodilatation; **Digestive:** flatulence, gastroesophageal reflux; **Musculoskeletal:** arthritis; **Nervous:** insomnia, nervousness, confusion; **Respiratory:** upper respiratory tract infection, cough, sinusitis, bronchitis, pharyngitis; **Skin:** dry skin, rash; **Urogenital:** impaired urination (hesitancy), increased post void residual volume, urinary retention, cystitis.

Adverse Events with Oxybutynin Chloride

Other adverse events have been reported with oxybutynin chloride: tachycardia, hallucinations, cycloplegia, mydriasis, impotence, and suppression of lactation.

OVERDOSAGE

The continuous release of oxybutynin from DITROPAN® XL should be considered in the treatment of overdosage. Patients should be monitored for at least 24 hours. Treatment should be symptomatic and supportive. Activated charcoal as well as a cathartic may be administered.

Overdosage with oxybutynin has been associated with anticholinergic effects including CNS excitation, flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention.

Ingestion of 100 mg oxybutynin chloride in association with alcohol has been reported in a 13 year old boy who experienced memory loss, and a 34 year old woman who developed stupor, followed by disorientation and agitation on awakening, dilated pupils, dry skin, cardiac arrhythmia, and retention of urine. Both patients fully recovered with symptomatic treatment.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from moisture and humidity.

Rx only.

Manufactured, distributed, and marketed by ALZA Corporation, Palo Alto, CA 94304.

Marketed by UCB Pharma, Inc., Smyrna, GA 30080.

0008960 Edition: 6/99

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0009063-1

be much lower in cases of polymicrobial infections, in which competing pathogens may inhibit growth to a diagnostic threshold.[43]

Blind bronchial sampling is less invasive, cheaper, and causes less compromise of gas exchange than other techniques, and does not require a trained bronchoscopist to perform. At least one study[44] found this approach to be comparable in accuracy to other, more-invasive bronchoscopic techniques, and another study[45] found it superior to protected brush biopsy because it was more sensitive and less invasive (TABLE 3).

PREVENTING NOSOCOMIAL PNEUMONIA

Respiratory therapy equipment

Contamination of the ventilator is an uncommon source of exposure to microorganisms associated with nosocomial pneumonia. However, circuit manipulation and use of in-line nebulized medication may occasionally introduce microorganisms and lead to pneumonia in hospitalized patients. Frequent circuit changes, ie, every 24 vs every 48 hours, are associated with a higher risk for infection.[17] Consequently, the Centers for Disease Control and Prevention (CDC) recommends rinsing nebulizers with sterile water or drying them with air between nebulizations.[46] It also recommends that reintubation be avoided whenever possible.

Selective decontamination of the digestive tract

One can try to decrease gastric and oropharyngeal colonization by aerobic Gram-negative organisms without disrupting the anaerobic flora by giving nonabsorbable antibiotics such as colistin sulphate, polymyxin E, and tobramycin and antifungal agents such as amphotericin B. These agents must be given both as a nasogastric suspension and as an oral paste. However, this procedure is cumbersome for patients and nurses alike. In addition its efficacy remains unproven, and it may actually encourage resistant organisms to evolve. Consequently, the latest CDC guidelines do not recommend its routine use.[46]

Reducing the risk of ventilator-associated pneumonia

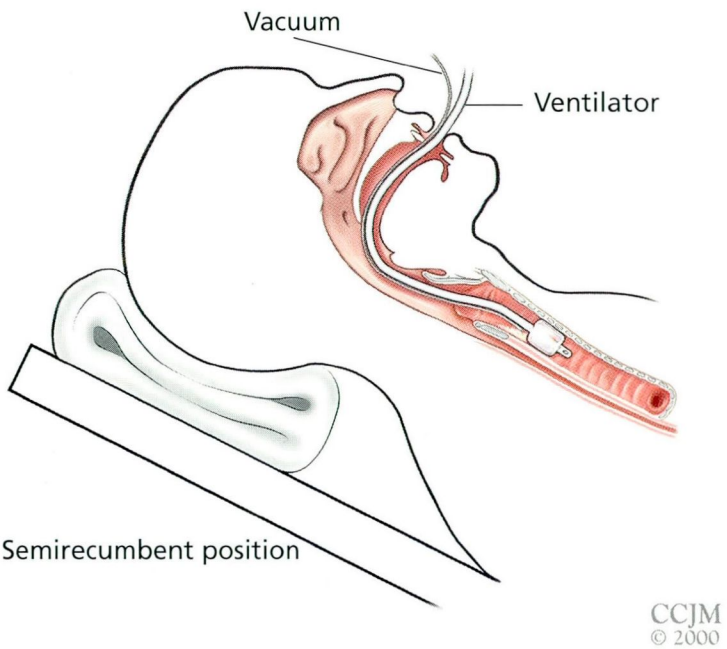

FIGURE 2. Continuous aspiration of pooled subglottal secretions. This technique greatly reduces the risk of ventilator-associated pneumonia caused by endogenous organisms. The endotracheal tube has an extra lumen that connects to a vacuum device. Placing the patient in a semirecumbent position helps prevent aspiration into the lower airway.

Nursing practices

Consistent handwashing between patient contacts is the basic principle of good infection control.[46]

Semirecumbent positioning of the patient is also recommended to prevent aspiration into the lower airway.[47]

Continuous aspiration of pooled subglottic secretions is a new technique involving an endotracheal tube with an extra lumen for this purpose.[48] This approach greatly reduces the rate of early nosocomial pneumonia caused by endogenous organisms[49] (FIGURE 2).

TREATMENT OF NOSOCOMIAL PNEUMONIA

Antibiotics are the mainstay of therapy. Supportive measures include supplemental

oxygen, bronchodilators, and chest physiotherapy.[11]

Early antibiotic therapy vs early bronchoscopy

Most patients with nosocomial pneumonia are critically ill. If antibiotics are to be life-saving, they must be started quickly. By identifying the pathogen early, bronchoscopy may help direct the choice of antimicrobial therapy and may prevent overdiagnosis of pneumonia (which commonly occurs when clinical criteria are used alone), thereby avoiding the expense and the undesirable effects of unnecessary antibiotic therapy.[11]

In some instances, however, bronchoscopy to obtain material for culture may lead to an unacceptable delay in starting antibiotic therapy. In addition, bronchoscopy in this setting is expensive and has limited value for patients who have already undergone antibiotic therapy. No randomized controlled trial has demonstrated improved outcomes in patients with suspected nosocomial pneumonia evaluated with bronchoscopy. Consequently, bronchoscopy is best reserved for patients with persistent lung infiltrates who fail to respond to initial therapy, or for subsets of patients with ventilator-associated pneumonia, although this latter role has not been well examined.[50]

Frequent changes of the mechanical ventilation circuit increase the risk of infection

Antibiotic selection

Several factors should influence antibiotic selection:

- The patient's laboratory microbiological data, if available
- The nosocomial pathogens prevalent in a nursing unit
- Local antimicrobial resistance patterns
- Prior antibiotic therapy
- Severity of the illness in the affected patient.

Although individual antibiotics may have a bacteriostatic or bactericidal effect, some bactericidal antibiotics (eg, aminoglycosides, quinolones) depend on high peak concentrations or have a post-antibiotic effect, while others (eg, beta-lactams) require a minimum inhibitory concentration for effect.

The degree of tissue penetration also must be considered. The capillary bed of the lung, for example, is not fenestrated and may therefore limit the penetration of less lipid-soluble antibiotics (eg, beta-lactams, aminoglycosides) compared with more lipophilic ones (eg, quinolones).

Empiric therapy involves broad-spectrum antibiotics, the selection of which is based on the severity of illness and the individual patient's risk for infection with *P aeruginosa*[51] (TABLE 4).

Monotherapy vs combination antibiotic therapy

Several studies have examined the comparative efficacy of monotherapy vs combination therapy. Controlled trials have shown that antibiotic monotherapy is as good as combination therapy in nongranulocytopenic patients,[11,51,52] except in suspected *Pseudomonas* and *Acinetobacter* infections, in which combination therapy is associated with a survival benefit.[52,53] This observation may be due to the synergistic effect of beta-lactams and aminoglycosides against *P aeruginosa*. Antibiotic resistance may also be an issue in cases of infection with *Pseudomonas* species, as use of monotherapy is associated with higher complication rates.[53]

While broad-spectrum antibiotics have made monotherapy possible, their indiscriminate use has also led to the emergence of opportunistic pathogens such as *Xanthomonas maltophilia*.[54] This organism is often grown as part of mixed cultures; therefore, distinguishing colonization from true infection can often be difficult. *X maltophilia* is usually resistant to extended-spectrum penicillins, cephalosporins, and fluoroquinolones and is almost always resistant to imipenem. However, it is almost universally susceptible to co-trimoxazole.

Nonintubated patients with nosocomial pneumonia who have never taken antibiotics and are not critically ill are usually infected with endogenous organisms (eg, *S pneumoniae*, *H influenza*) and frequently improve with monotherapy. Critically ill intubated patients who have received antibiotics at some point during their hospital stay

OFFICIAL COURT NOTICE

Attention

Physicians and Pharmacies with "Fen-Phen," Pondimin® and/or Redux™ Patients

IMPORTANT NOTICE

- **If your patient took the diet drugs Pondimin® and/or Redux™, or**
- **If your patient took the diet drug combination popularly known as "Fen-Phen," *you should read this information.***

Thousands of consumers throughout the country have filed lawsuits claiming that they were injured or placed at an increased risk of injury as a result of taking Pondimin®, Redux™ and/or "Fen-Phen." These lawsuits claim, among other things, that taking the diet drugs Pondimin® and/or Redux™, or the combination of drugs known as "Fen-Phen," may produce lesions or abnormalities in the heart valves of some people. These lesions can cause abnormal blood flow in the heart which may be harmful depending on the level of abnormal blood flow. Such heart valve disease may be without symptoms, but it can be diagnosed through an "echocardiogram." American Home Products Corporation ("AHP") was responsible for the sale of Pondimin® and/or Redux™. AHP has defended vigorously against plaintiffs' lawsuits and disputes the plaintiffs' claims.

There is a proposed CLASS ACTION SETTLEMENT with AHP that gives all users of these diet drugs the right to receive money, medical testing services, and/or other benefits, depending on the diet drug user's circumstances. These benefits are summarized in the chart below.

MEMBERS OF THE CLASS HAVE THE FOLLOWING RIGHTS:

1. The right to choose an "Accelerated Implementation Option" which will allow them to begin receiving Settlement Benefits quickly, regardless of whether the Settlement receives Final Judicial Approval;
2. The right to receive Settlement Benefits in the event that the Settlement receives Final Judicial Approval, if they "Register" for these benefits on time;
3. The right to appear at a hearing on May 1-5, 2000, at the United States District Court, 601 Market Street, Philadelphia, PA 19106 and object to the settlement; and
4. The right to exclude themselves ("opt-out") from the Settlement.

A detailed Notice Package has been prepared which contains the information that your patients should have to determine how the proposed Settlement affects them. The Notice Package also contains forms that your patients must complete in order to "Register" and receive Settlement Benefits, accept the Accelerated Implementation Option, or opt-out of the Settlement.

If your patients take no action before March 30, 2000, they will remain in the Settlement and be bound by its terms even if they are a member of another certified class.

Your patients can request a copy of the Notice Package by calling the following telephone number: 1-800-386-2070. They can also request a copy of the Notice Package on the Worldwide Web at the following web address: www.settlementdietdrugs.com. They can also view the Notice Package at the same web address.

Summary of Settlement Benefits	People Who Used "Fen-Phen," Pondimin® and/or Redux™ for 61 or More Days	People Who Used "Fen-Phen," Pondimin® and/or Redux™ for 60 Days or Less
Refund: $30/month for use of Pondimin® $60/month for use of Redux™	YES (subject to $500 limit and availability of funds after pay-out of other benefits to class)	YES
Free echocardiogram and appointment with doctor to discuss the results	YES	Generally NO, but with exceptions, including humanitarian or compassionate reasons or true financial hardship
Cash or medical services benefit for heart valve disease according to "FDA Positive" criteria	$6,000 in CASH or $10,000 in heart valve related MEDICAL SERVICES	$3,000 in CASH or $5,000 in heart valve related MEDICAL SERVICES
"Matrix" compensation benefits for serious valvular heart disease as described in the brochure titled "Settlement Matrix Compensation Benefits Guide" (before Court authorized deductions)	Between $7,389 and $1,485,000 depending on age and level of severity	Between $7,389 and $297,000 depending on age and level of severity
Medical registry to "Track" condition of Pondimin® and/or Redux™ users for purposes of research and education	YES	YES
Establishment of a fund for medical research and education concerning cardiovascular disease	YES	YES

The United States District Court for the Eastern District of Pennsylvania has directed the publication of this Notice.
This Official Notice is not an expression of any opinion of the Court regarding the merits of the litigation and does not reflect findings of fact by the Court.

TABLE 4

Empiric antibiotic therapy in nosocomial pneumonia

Mild to moderately ill patients or patients at a low risk of *Pseudomonas* infection

- Monotherapy
  - Second-generation cephalosporins (eg, cefuroxime, cefamandole)
  - Nonpseudomonal third-generation cephalosporins (eg, ceftriaxone, cefotaxime)
  - Ampicillin-sulbactam
  - Fluoroquinolones (eg, ciprofloxacin)
    - Caution: poor activity against *Streptococcus*, anaerobes, and other Gram-positive bacteria; for penicillin-allergic patients
  - Trimethoprim-sulfamethoxazole (for penicillin-allergic patients)
- Dual therapy
  - Any of the above plus an aminoglycoside

Critically ill patients or those at high risk for *Pseudomonas* infection

- Antipseudomonal penicillin plus an aminoglycoside
- Antipseudomonal penicillin with beta-lactamase inhibitor (eg, ticarcillin-clavulanate) plus an aminoglycoside
- Third-generation antipseudomonal cephalosporin (eg, ceftazidime and cefoperazone) plus an aminoglycoside
- A fluoroquinolone plus a beta-lactam
- Imipenem plus an aminoglycoside
- A fluoroquinolone plus an aminoglycoside (for penicillin-allergic patients)

Special coverage

- Clindamycin or metronidazole to treat anaerobic bacteria in patients at risk of aspiration
- Vancomycin for methicillin-resistant *Staphylococcus aureus* in young patients, patients with diabetes, intravenous drug abuse, or recent influenza infection
- High-dose erythromycin, azithromycin, or ciprofloxacin for patients at risk of *Legionella* infection

If antibiotics are to be life-saving, they must be started quickly

are more commonly colonized with Gram-negative organisms when nosocomial pneumonia develops, and they benefit from combination chemotherapy.

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The once-a-day metoprolol for 24-hour coverage*

*Indicated for hypertension and angina.

As with most beta-blocking agents, Toprol-XL is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. Patients taking Toprol-XL should avoid abrupt cessation of therapy. Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. The dosage should be reduced gradually over a 1-2 week period while monitoring patients. Please see brief summary of package insert, including Box Warning, below.

TOPROL-XL® TABLETS

(metoprolol succinate)

Extended Release Tablets

Tablets: 50 mg, 100 mg, and 200 mg

Brief Summary: For full prescribing information, see package insert.

INDICATIONS AND USAGE

Hypertension

Toprol-XL tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

Angina Pectoris

Toprol-XL tablets are indicated in the long-term treatment of angina pectoris.

CONTRAINDICATIONS

Hypertension and Angina

Toprol-XL is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS

Hypertension and Angina

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Toprol-XL should be administered cautiously. Both digitalis and Toprol-XL slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Toprol-XL should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Toprol-XL, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1–2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Toprol-XL administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Toprol-XL therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative beta$_1$-selectivity, however, Toprol-XL may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$-selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Toprol-XL should be used (see DOSAGE AND ADMINISTRATION).

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Toprol-XL like other beta-blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta-blockers.

Diabetes and Hypoglycemia: Toprol-XL should be used with caution in diabetic patients if a beta-blocking agent is required. Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade, which might precipitate a thyroid storm.

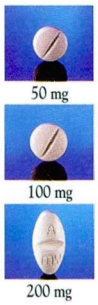
PRECAUTIONS

General

Toprol-XL should be used with caution in patients with impaired hepatic function.

Information for Patients

Patients should be advised to take Toprol-XL regularly and continuously, as directed, preferably with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Toprol-XL without consulting the physician. Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Toprol-XL has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Toprol-XL.



Convenience ▼ Compliance ▼ Consistent 24-Hour β_1-Blockade

Laboratory Tests

Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions

Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Toprol-XL plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg/day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg/day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed on metoprolol tartrate (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) and metoprolol succinate (a Salmonella/mammalian-microsome mutagenicity test) were negative.

No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C

Metoprolol tartrate has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Metoprolol is excreted in breast milk in very small quantities. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Toprol-XL is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Risk Of Anaphylactic Reactions

While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

ADVERSE REACTIONS

Hypertension and Angina

Most adverse effects have been mild and transient. The following adverse reactions have been reported for metoprolol tartrate.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, somnolence, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; syncope; chest pain; and hypotension have been reported in about 1 of 100 patients (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see WARNINGS).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, digestive tract disorders and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, decreased libido and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with metoprolol.

Potential Adverse Reactions

A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Toprol-XL.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE

Acute Toxicity

There have been a few reports of overdosage with Toprol-XL and no specific overdosage information was obtained with this drug, with the exception of animal toxicology data. However, since Toprol-XL (metoprolol succinate salt) contains the same active moiety, metoprolol, as conventional metoprolol tablets (metoprolol tartrate salt), the recommendations on overdosage for metoprolol conventional tablets are applicable to Toprol-XL.

Signs and Symptoms

Potential signs and symptoms associated with overdosage with metoprolol are bradycardia, hypotension, bronchospasm, and cardiac failure.

Treatment

There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly. On the basis of the pharmacologic actions of metaprolol tartrate, the following general measures should be employed.

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.

Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretics should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol or glucagon may be considered.

DOSAGE AND ADMINISTRATION

Toprol-XL is an extended release tablet intended for once-a-day administration. When switching from immediate release metoprolol tablet to Toprol-XL, the same total daily dose of Toprol-XL should be used.

As with immediate release metoprolol, dosages of Toprol-XL should be individualized and titration may be needed in some patients.

Toprol-XL tablets are scored and can be divided; however, the whole or half tablet should be swallowed whole and not chewed or crushed.

Hypertension

The usual initial dosage is 50 to 100 mg daily in a single dose, whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. Dosages above 400 mg per day have not been studied.

Angina Pectoris

The dosage of Toprol-XL should be individualized. The usual initial dosage is 100 mg daily, given in a single dose. The dosage may be gradually increased at weekly intervals until optimum clinical response has been obtained or there is a pronounced slowing of the heart rate. Dosages above 400 mg per day have not been studied. If treatment is to be discontinued, the dosage should be reduced gradually over a period of 1–2 weeks (see WARNINGS).

HOW SUPPLIED

Tablets 50 mg:
Contain 47.5 mg of metoprolol succinate equivalent to 50 mg of metoprolol tartrate, USP
Are white, biconvex, round, film-coated
Engraved A|no on one side and scored on the other
Bottles of 100 NDC 0186-1090-05

Tablets 100 mg:
Contain 95 mg of metoprolol succinate equivalent to 100 mg of metoprolol tartrate, USP
Are white, biconvex, round, film-coated
Engraved A|ms on one side and scored on the other
Bottles of 100 NDC 0186-1092-05

Tablets 200 mg:
Contain 190 mg of metoprolol succinate equivalent to 200 mg of metoprolol tartrate, USP
Are white, biconvex, oval, film-coated
Engraved A|my and scored on one side
Bottles of 100 NDC 0186-1094-05

Store at controlled room temperature 15°–30°C (59°–86°F).

Manufactured by:
Astra Pharmaceutical Production, AB
Södertälje, Sweden

Manufactured for:

Rev. 9/98
021671R38

ASTRA® Astra USA, Inc., Westborough, MA 01581

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ADDRESS: *David Litaker, MD, MSc, Department of General Internal Medicine, A72, 9500 Euclid Avenue, Cleveland, OH 44195, e-mail litaked@ccf.org.*

PLAVIX®
clopidogrel bisulfate tablets

BRIEF SUMMARY — Please see package insert for full prescribing information.
INDICATIONS AND USAGE: PLAVIX (clopidogrel bisulfate) is indicated for the reduction of atherosclerotic events (myocardial infarction, stroke, and vascular death) in patients with atherosclerosis documented by recent stroke, recent myocardial infarction, or established peripheral arterial disease.
CONTRAINDICATIONS: Plavix is contraindicated in patients with a hypersensitivity to the drug substance or any component of the product, and those with active pathologic bleeding such as peptic ulcer or intracranial hemorrhage.
WARNINGS: None.
PRECAUTIONS: General: As with other antiplatelet agents, PLAVIX should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions. If a patient is to undergo elective surgery and an antiplatelet effect is not desired, PLAVIX should be discontinued 7 days prior to surgery. *GI Bleeding:* PLAVIX prolongs the bleeding time. In CAPRIE, PLAVIX was associated with a rate of gastrointestinal bleeding of 2.0%, vs. 2.7% on aspirin. PLAVIX should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions (such as aspirin and other nonsteroidal anti-inflammatory drugs [NSAIDs]) should be used with caution in patients taking PLAVIX. *Use in Hepatically Impaired Patients:* Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses. PLAVIX should be used with caution in this population.
Information for Patients: Patients should be told that it may take them longer than usual to stop bleeding when they take PLAVIX, and that they should report any unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking PLAVIX before any surgery is scheduled and before any new drug is taken.
Drug Interactions: Study of specific drug interactions yielded the following results: *Aspirin:* Aspirin did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation. Concomitant administration of 500 mg of aspirin twice a day for 1 day did not significantly increase the prolongation of bleeding time induced by PLAVIX. PLAVIX potentiated the effect of aspirin on collagen-induced platelet aggregation. The safety of chronic concomitant administration of aspirin and PLAVIX has not been established. *Heparin:* In a study in healthy volunteers, PLAVIX did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Coadministration of heparin had no effect on inhibition of platelet aggregation induced by PLAVIX. The safety of this combination has not been established, however, and concomitant use should be undertaken with caution. *Nonsteroidal Anti-Inflammatory Drugs (NSAIDs):* In healthy volunteers receiving naproxen, concomitant administration of PLAVIX was associated with increased occult gastrointestinal blood loss. NSAIDs and PLAVIX should be coadministered with caution. *Warfarin:* The safety of the coadministration of PLAVIX with warfarin has not been established. Consequently, concomitant administration of these two agents should be undertaken with caution. (See **Precautions-General**). *Other Concomitant Therapy:* No clinically significant pharmacodynamic interactions were observed when PLAVIX was coadministered with **atenolol, nifedipine,** or both atenolol and nifedipine. The pharmacodynamic activity of PLAVIX was also not significantly influenced by the coadministration of **phenobarbital, cimetidine** or **estrogen**. The pharmacokinetics of **digoxin** or **theophylline** were not modified by the coadministration of PLAVIX (clopidogrel bisulfate). At high concentrations *in vitro*, clopidogrel inhibits P_{450} (2C9). Accordingly, PLAVIX may interfere with the metabolism of **phenytoin, tamoxifen, tolbutamide, warfarin, torsemide, fluvastatin,** and many **nonsteroidal anti-inflammatory agents,** but there are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is coadministered with PLAVIX. In addition to the above specific interaction studies, patients entered into CAPRIE received a variety of concomitant medications **including diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents, antiepileptic agents** and **hormone replacement therapy** without evidence of clinically significant adverse interactions.
Drug/Laboratory Test Interactions: None known.
Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no evidence of tumorigenicity when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats at dosages up to 77 mg/kg per day, which afforded plasma exposures >25 times that in humans at the recommended daily dose of 75 mg. Clopidogrel was not genotoxic in four *in vitro* tests (Ames test, DNA-repair test in rat hepatocytes, gene mutation assay in Chinese hamster fibroblasts, and metaphase chromosome analysis of human lymphocytes) and in one *in vivo* test (micronucleus test by oral route in mice). Clopidogrel was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg per day (52 times the recommended human dose on a mg/m^2 basis).
Pregnancy: Pregnancy Category B. Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day (respectively, 65 and 78 times the recommended daily human dose on a mg/m^2 basis), revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, PLAVIX should be used during pregnancy only if clearly needed.
Nursing Mothers: Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the nursing woman.
Pediatric Use: Safety and effectiveness in the pediatric population have not been established.
ADVERSE REACTIONS: PLAVIX (clopidogrel bisulfate) has been evaluated for safety in more than 11,300 patients, including over 7,000 patients treated for 1 year or more. The overall tolerability of PLAVIX was similar to that of aspirin regardless of age, gender and race, with an approximately equal incidence (13%) of patients withdrawing from treatment because of adverse reactions. The clinically important adverse events observed in CAPRIE are discussed below.

Hemorrhagic: In patients receiving PLAVIX in CAPRIE, gastrointestinal hemorrhage occurred at a rate of 2.0%, and required hospitalization in 0.7%. In patients receiving aspirin, the corresponding rates were 2.7% and 1.1%, respectively. The incidence of intracranial hemorrhage was 0.4% for PLAVIX compared to 0.5% for aspirin. *Neutropenia/agranulocytosis:* Ticlopidine, a drug chemically similar to PLAVIX, is associated with a 0.8% rate of severe neutropenia (less than 450 neutrophils/μL). Patients in CAPRIE were intensively monitored for neutropenia. Severe neutropenia was observed in six patients, four on PLAVIX and two on aspirin. Two of the 9599 patients who received PLAVIX and none of the 9586 patients who received aspirin had neutrophil counts of zero. One of the four PLAVIX patients was receiving cytotoxic chemotherapy, and another recovered and returned to the trial after only temporarily interrupting treatment with PLAVIX. Although the risk of myelotoxicity with PLAVIX thus appears to be quite low, this possibility should be considered when a patient receiving PLAVIX demonstrates fever or other sign of infection. *Gastrointestinal:* Overall, the incidence of gastrointestinal events (e.g., abdominal pain, dyspepsia, gastritis and constipation) in patients receiving PLAVIX was 27.1%, compared to 29.8% in those receiving aspirin. The incidence of peptic, gastric or duodenal ulcers was 0.7% for PLAVIX and 1.2% for aspirin. Cases of diarrhea were reported in 4.5% of patients in the PLAVIX group compared to 3.4% in the aspirin group. However, these were rarely severe (PLAVIX = 0.2% and aspirin = 0.1%). The incidence of patients withdrawing from treatment because of gastrointestinal adverse reactions was 3.2% for PLAVIX and 4.0% for aspirin. *Rash and Other Skin Disorders: The incidence of skin and appendage disorders in patients receiving* PLAVIX was 15.8% (0.7% serious); the corresponding rate in aspirin patients was 13.1% (0.5% serious). The overall incidence of patients withdrawing from treatment because of skin and appendage disorders adverse reactions was 1.5% for PLAVIX and 0.8% for aspirin. Adverse events occurring in ≥2.5% of patients on PLAVIX in the CAPRIE controlled clinical trial are shown below regardless of relationship to PLAVIX. The median duration of therapy was 20 months, with a maximum of 3 years.

Adverse Events Occurring in ≥ 2.5% of PLAVIX Patients

	% Incidence	(% Discontinuation)
Body System **Event**	**PLAVIX [n=9599]**	**Aspirin [n=9586]**
Body as a Whole - general disorders		
Chest Pain	8.3 (0.2)	8.3 (0.3)
Accidental Injury	7.9 (0.1)	7.3 (0.1)
Influenza-like symptoms	7.5 (<0.1)	7.0 (<0.1)
Pain	6.4 (0.1)	6.3 (0.1)
Fatigue	3.3 (0.1)	3.4 (0.1)
Cardiovascular disorders, general		
Edema	4.1 (<0.1)	4.5 (<0.1)
Hypertension	4.3 (<0.1)	5.1 (<0.1)
Central & peripheral nervous system disorders		
Headache	7.6 (0.3)	7.2 (0.2)
Dizziness	6.2 (0.2)	6.7 (0.3)
Gastrointestinal system disorders		
Abdominal pain	5.6 (0.7)	7.1 (1.0)
Dyspepsia	5.2 (0.6)	6.1 (0.7)
Diarrhea	4.5 (0.4)	3.4 (0.3)
Nausea	3.4 (0.5)	3.8 (0.4)
Metabolic & nutritional disorders		
Hypercholesterolemia	4.0 (0)	4.4 (<0.1)
Musculo-skeletal system disorders		
Arthralgia	6.3 (0.1)	6.2 (0.1)
Back Pain	5.8 (0.1)	5.3 (<0.1)
Platelet, bleeding, & clotting disorders		
Purpura	5.3 (0.3)	3.7 (0.1)
Epistaxis	2.9 (0.2)	2.5 (0.1)
Psychiatric disorders		
Depression	3.6 (0.1)	3.9 (0.2)
Respiratory system disorders		
Upper resp tract infection	8.7 (<0.1)	8.3 (<0.1)
Dyspnea	4.5 (0.1)	4.7 (0.1)
Rhinitis	4.2 (0.1)	4.2 (<0.1)
Bronchitis	3.7 (0.1)	3.7 (0)
Coughing	3.1 (<0.1)	2.7 (<0.1)
Skin & appendage disorders		
Rash	4.2 (0.5)	3.5 (0.2)
Pruritus	3.3 (0.3)	1.6 (0.1)
Urinary system disorders		
Urinary tract infection	3.1 (0)	3.5 (0.1)

Incidence of discontinuation, regardless of relationship to therapy, is shown in parentheses.

Other adverse experiences of potential importance occurring in 1% to 2.5% of patients receiving PLAVIX in the CAPRIE controlled clinical trial are listed below regardless of relationship to PLAVIX. In general, the incidence of these events was similar in the aspirin-treated group. *Autonomic Nervous System Disorders:* Syncope, Palpitation. *Body as a Whole - general disorders:* Asthenia, Hernia. *Cardiovascular disorders:* Cardiac failure. *Central and peripheral nervous system disorders:* Cramps legs, Hypoaesthesia, Neuralgia, Paraesthesia, Vertigo. *Gastrointestinal system disorders:* Constipation, Vomiting. *Heart rate and rhythm disorders:* Fibrillation atrial. *Liver and biliary system disorders:* Hepatic enzymes increased. *Metabolic and nutritional disorders:* Gout, hyperuricemia, non-protein nitrogen (NPN) increased. *Musculoskeletal system disorders:* Arthritis, Arthrosis. *Platelet, bleeding & clotting disorders:* GI hemorrhage, hematoma, platelets decreased. *Psychiatric disorders:* Anxiety, Insomnia. *Red blood cell disorders:* Anemia. *Respiratory system disorders:* Pneumonia, Sinusitis. *Skin and appendage disorders:* Eczema, Skin ulceration. *Urinary system disorders:* Cystitis. *Vision disorders:* Cataract, Conjunctivitis. Other potentially serious adverse events which may be of clinical interest but were rarely reported (< 1%) in patients who received PLAVIX are listed below regardless of relationship to PLAVIX. In general, the incidence of these events was similar in the aspirin group. *Body as a whole:* Allergic reaction, necrosis ischemic. *Cardiovascular disorders:* Edema generalized. *Gastrointestinal system disorders:* Gastric ulcer perforated, gastritis hemorrhagic, upper GI ulcer hemorrhagic. *Liver and Biliary system disorders:* Bilirubinemia, hepatitis infectious, liver fatty. *Platelet, bleeding and clotting disorders:* hemarthrosis, hematuria, hemoptysis, hemorrhage intracranial, hemorrhage retroperitoneal, hemorrhage of operative wound, ocular hemorrhage, pulmonary hemorrhage, purpura allergic, thrombocytopenia. *Red blood cell disorders:* Anemia aplastic, anemia hypochromic. *Reproductive disorders, female:* Menorrhagia. *Respiratory system disorders:* Hemothorax. *Skin and appendage disorders:* Bullous eruption, rash erythematous, rash maculopapular, urticaria. *White cell and reticuloendothelial system disorders:* Agranulocytosis, granulocytopenia, leukemia, leukopenia, neutrophils decreased.
OVERDOSAGE: One case of deliberate overdosage with PLAVIX (clopidogrel bisulfate) was reported in the large, controlled clinical study. A 34-year-old woman took a single 1,050-mg dose of PLAVIX (equivalent to 14 standard 75-mg tablets). There were no associated adverse events. No special therapy was instituted, and she recovered without sequelae. No adverse events were reported after single oral administration of 600 mg (equivalent to 8 standard 75-mg tablets) of PLAVIX in healthy volunteers. The bleeding time was prolonged by a factor of 1.7, which is similar to that typically observed with the therapeutic dose of 75 mg of PLAVIX per day. A single oral dose of clopidogrel at 1500 or 2000 mg/kg was lethal to mice and to rats and at 3000 mg/kg to baboons. Symptoms of acute toxicity were vomiting (in baboons), prostration, difficult breathing, and gastrointestinal hemorrhage in all species.
Recommendations About Specific Treatment: Based on biological plausibility, platelet transfusion may be appropriate to reverse the pharmacological effects of PLAVIX if quick reversal is required.
DOSAGE AND ADMINISTRATION: The recommended dose of PLAVIX is 75 mg once daily with or without food.

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