

Medication Safety Update

WARFARIN ADVERSE DRUG REACTIONS

Warfarin is an oral anticoagulant that was originally approved by the Food and Drug Administration in 1954, and remains the most widely used oral anticoagulant to prevent and treat thromboembolic disease.

Because of its mechanism of action, warfarin has long been known to have significant hemorrhagic risks. In October 2006, a black box warning was added to the prescribing information concerning the risk

of major and sometimes fatal bleeding associated with warfarin therapy. Warfarin inhibits the synthesis of vitamin K-dependent coagulation factors II, VII, IX, and X and

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Policy Update

LOOK-ALIKE SOUND ALIKE DRUGS

Look-alike and sound-alike drugs pose a significant risk within the healthcare system. Drugs that look or sound like other drugs can lead to harmful and potentially fatal medication errors.¹ With the vast number of brand and generic drugs

currently on the market, there is noteworthy potential for errors resulting from similar or confusing drug names.² Factors which contribute to look-alike and sound-alike medication errors include poor handwriting, lack of knowledge of new drug

products, similar packaging or labeling, incorrect selection of drugs from a computerized list, misinterpretation and/or poor communication of verbal orders, and incomplete knowledge of drug names.^{1,2} Therefore, it is important that all

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Therapy Update

SEXUALLY TRANSMITTED DISEASES TREATMENT UPDATE

Treatment in the area of sexually transmitted disease continues to evolve. The Centers for Disease Control and Prevention (CDC), in conjunction with an expert panel, released an update to the *Guidelines for Treatment of Sexually Transmitted Diseases* in 2002. New clinical evidence

has amassed since that time predicated an update to these recommendations.

The *Sexually Transmitted Disease Treatment Guidelines, 2006* make new recommendations in a number of areas relevant to pharmacotherapy.

In the past four years, new evidence in the area of trichomoniasis treatment has been released. In 2002, both the recommended and alternative regimens for treatment were metronidazole based. Randomized controlled trials

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FDA Fast Facts

METHADONE SAFETY

Reports of respiratory depression and cardiac arrhythmias in patients receiving methadone have been received. These adverse events are the result of methadone overdoses, drug interactions, and cardiac toxicities (e.g., QT prolongation and Torsades de Pointes). The analgesic effect of methadone lasts about 4 to 8 hours. Methadone stays in the body up to 59 hours. Accumulation occurs leading to dose dependent adverse effects.

ULTRALENTE/LENTE

As of 2005, Eli Lilly decided to stop the production of Humulin U and Humulin L due to a 70% decline in their use over the past five years. Less than 2% of patients on insulin are predicted to be affected. Current recommendations are for patients to be switched to NPH human insulin or a basal insulin analog. Upon switching, careful monitoring of blood glucose levels and insulin therapy adjustments are important.

USE OF HOME MEDS

A "continue home medications" order is not considered a valid order; prescribers must list home medications, dose, route, and schedule individually on admission or discharge orders. Medications brought from home cannot be administered to the patient when the medication is available from the pharmacy and only medications of assured quality and safety shall be administered.

The role of
azithromycin
for chlamydial
infections
during
pregnancy has
expanded based
on new clinical
evidence

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anticoagulant proteins C and S. This mechanism is dose dependent, and the full anticoagulant effect of a dose may not be seen for several days. Clinicians often wait one week to evaluate dosing changes by monitoring the International Normalized Ratio (INR) and the prothrombin time for therapeutic effect. Warfarin has a narrow therapeutic window necessitating careful management for safety and efficacy. If needed the action of warfarin may be overcome by the administration of vitamin K or by transfusion of plasma proteins that contain clotting factors. Management of warfarin is further complicated due to factors such as, patient compliance, acute patient changes, alcohol consumption, liver disease, and significant interactions with vitamin K containing foods and other medications.

In the management of warfarin, many factors are beyond a practitioner's control. Medication interactions are important and often not recognized for their potential influence on safety and efficacy. At The Medical Center, 132 warfarin adverse drug reactions have been reported over the past 14 years, and these represent only a fraction of all interactions because many are unreported. Of the reported interactions, over 95% occurred prior to hospitalization suggesting that extensive patient education, routine monitoring, and the identification of potential drug-drug interactions on the outpatient side should be a prevention strategy in the management of patients receiving warfarin.

Currently, the pharmacy department has several initiatives and pilot projects looking into improving warfarin use and reducing adverse drug reactions. These include evaluating the inpatient ordering process of warfarin, improving deep vein thrombosis assessment and prophylaxis, and measuring the impact of discharge counseling in conjunction with follow up education after discharge for certain drugs including warfarin. Pharmacy invites consults for the management of inpatients on warfarin and referrals to pharmacy anticoagulation

services for the family practice, indigent care, and long-term-care patients of Columbus Regional Health System.

A major focus of pharmacy's anticoagulation clinics and services is the screening for potential drug-drug interactions. To screen for clinically significant potential medication interactions it is important to take a complete medication history including over-the-counter and herbal products as patients often do not voluntarily report their use.

Although warfarin has the potential for severe adverse reactions, it can be used safely with proper education and monitoring

Possibly the most difficult group of drugs to manage for a patient taking warfarin are those medications that potentiate bleeding risk independent of INR. This is an issue with other anticoagulants, antiplatelet drugs, and non-steroidal anti-inflammatory drugs including the COX-2 selective agents.

Another group of drugs to use cautiously are those that interact with the liver's cytochrome P-450 (CYP) system. Warfarin's more potent S-isomer is metabolized by the (CYP) 2C9 pathway and the R-isomer is metabolized by the (CYP) 1A2 and the 3A4 pathway. Therefore any medications that induce or inhibit these pathways have a potential to interact with warfarin.

Although literature is poor regarding specific mechanisms and quantitative information, a compilation of data from case reports and studies implicate several drug classes and individual drugs as repeat offenders with clinically significant interactions. Anti-infective agents,

particularly the imidazoles, macrolides, quinolones, cotrimoxazole, isoniazid and rifampin are often reported. Other problematic groups include cardiovascular and lipid lowering agents such as aspirin, acetylsalicylic acid, clopidogrel, dipyridamole, sulfapyrazone, ticlopidine, heparin, amiodarone, HMG-CoA reductase inhibitors and fibric acid derivatives. The serotonin selective re-uptake inhibitors, and the acid reducers omeprazole and cimetidine are often implicated in warfarin adverse reaction case reports. These are just some of the more prevalent interactions that are common. Because of the difficult nature and complexity of drug interactions, it is recommended that patients started on warfarin or those with drug therapy regimen changes be screened for potential interactions and monitored more frequently. Available to all practitioners through OASIS under medical access are the references Clinical Pharmacology and Micromedex. Both resources have interactive programs to screen for potential interactions between multiple drugs on each search. Also included as an insert to the pharmacy bulletin is a table of clinically significant drug interactions with warfarin to assist decision making.

Although warfarin has a narrow therapeutic window with the potential for severe adverse reactions, it can be safe and effective when used with the proper education and monitoring. Being aware of potential drug interactions and acting proactively is important to give patients quality care and event free anticoagulation therapy. Please contact the drug information center with any questions regarding anticoagulation management or utilization of available resources.

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STD GUIDELINE UPDATE

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comparing tinidazole to metronidazole (both of which are members of the nitroimidazole drug class) show that tinidazole is equivalent or superior to metronidazole when measured by both parasitologic cure and symptom resolution. Tinidazole is now FDA approved for the treatment of this condition. The new guidelines acknowledge tinidazole as a recommended treatment option in addition to metronidazole. Tinidazole is useful in metronidazole treatment failure because many isolates have lower minimum inhibitory concentrations (MICs) to tinidazole than metronidazole. Tinidazole is an option for recurrent cases of trichomoniasis. However, due to experience, tolerability, efficacy and acquisition cost, metronidazole remains first line therapy. For recurrence of infection, consider administering metronidazole in a single dose orally. In the setting of treatment failure of single dose metronidazole when reinfection is excluded, metronidazole as a week long course or tinidazole as a single dose are appropriate choices. Remember that tinidazole's safety in pregnant women has not been evaluated in clinical practice.

The role of azithromycin for chlamydial infections during pregnancy has expanded based on new clinical evidence. At the time the 2002 guidelines were published, azithromycin was considered an alternative treatment for this indication because of limited evidence. Erythromycin or amoxicillin were the recommended treatments. The problem with erythromycin based regimens is intolerable gastrointestinal side effects that interfere with compliance. More evidence from both clinical experience and studies has been amassed documenting azithromycin efficacy. The new recommendations are that azithromycin can be considered a first line treatment option in addition to amoxicillin. Erythromycin based regimens are considered alternatives. Repeat testing for the presence of chlamydia three weeks after therapy completion should be performed regardless of which regimen is chosen.

The role of *M. genitalium* and trichomoniasis in urethritis and cervicitis has been re-evaluated since the guidelines were last published. An increasing proportion of patients are presenting with

non-gonococcal urethritis (NGU) not caused by *C. trachomatis*. Recognition of the role of *M. genitalium* and *T. vaginalis* as causative agents in these cases has increased. While the recommended regimens for NGU remain azithromycin and doxycycline, evidence shows that *M. genitalium* may respond better to azithromycin. In cases of NGU treatment failure or where contact with trichomoniasis is suspected, it is recommended to test for the presence of *T. vaginalis*. In the past, regimens combining metronidazole and erythromycin or erythromycin alone were recommended for treatment failure. With new evidence for azithromycin and tinidazole efficacy for *M. genitalium* and *T. vaginalis* respectively, the new recommendations are for metronidazole plus azithromycin or tinidazole plus azithromycin. In this setting, metronidazole should be utilized before tinidazole. Exclude the azithromycin option if it was used initially.

While *C. trachomatis* and *N. gonorrhoeae* are still the most likely causes of cervicitis, the role of other organisms has been increasingly recognized. Limited data show *M. genitalium* to be a possible pathogen. The recommended regimen for treatment remains azithromycin or doxycycline for non-gonococcal cervicitis. More consideration has been granted to the contribution of trichomoniasis in the presence of cervicitis. It is recommended to test for the presence of this and treat if applicable in patients presenting with cervicitis.

Further data on the resistance of *N. gonorrhoeae* to quinolones has been collected since 2002 through the CDC's Gonococcal Isolate Surveillance Project (GISP). Quinolones were previously not recommended for gonorrhea acquired in Asia and the Pacific (including Hawaii). As resistance has spread both internationally and to California, the new guidelines recommend avoiding quinolones in infections acquired while traveling abroad as well as in California. Quinolones are not recommended in men who have sex with men (MSM) because of the high prevalence of quinolone resistance in this population. Resistance continues to spread to urban

areas nationwide. Prevalence in the Southeast, excluding Miami, is still low.

The role of azithromycin in the treatment of syphilis in patients with a penicillin allergy has diminished based on new clinical evidence. In the 2002 guidelines, preliminary data showed that azithromycin was effective in patients with primary or secondary syphilis when a penicillin allergy excluded first-line treatment. In the past four years, several cases have been reported documenting azithromycin failure. Treponemal strains obtained from Seattle, San Francisco, and Baltimore contained a mutation that conferred azithromycin resistance. Clinical trials further addressing this issue are currently ongoing. As previously recommended in the 2002 guidelines, anytime alternative therapy is used for syphilis close follow-up is required. Azithromycin should never be used in latent, tertiary, or neurosyphilis. Data remains insufficient to recommend azithromycin for syphilis in pregnant women or in HIV-infected patients.

The recommendations for post exposure prophylaxis after sexual assault have changed since the guidelines were last published. Post exposure hepatitis B vaccination with follow up doses to complete the series and empiric antimicrobial coverage with a combination of ceftriaxone, metronidazole, and azithromycin or doxycycline alone is still recommended. A recommendation for emergency contraception to prevent pregnancy from the assault has been added. The efficacy of this regimen remains unevaluated.

Over the past four years, the combination of clinical experience and trial evidence has resulted in changes to how sexually transmitted diseases should be treated. New pharmacotherapy options and changes in resistance patterns are evidence to how rapidly the landscape of treatment can change. Clinicians must now combine clinical evidence with the above recommendations to provide the best possible care until the next update is published.

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The Pharmacy Bulletin is a service of the Department of Pharmacy Services. Its purpose is to disseminate information on drug therapy, additions and deletions from the drug Formularies, current excerpts from the literature regarding drug usage, FDA warnings, and adverse reactions. This newsletter will also inform practitioners of policies and procedures regarding drug usage. The inclusion of a product name in this publication, or information on a product, should not be construed as an endorsement of that product. Material in this publication may not be reprinted without written permission of Columbus Regional Healthcare System, Department of Pharmacy Services.

LOOK-ALIKE SOUND ALIKE DRUGS, continued from page 1

healthcare professionals maintain awareness of medications with the potential for these types of errors and implement work practices that ensure the safety of each patient.¹ Some of these work practices include:

- Store look-alike and sound-alike drugs in an alternate location in pharmacies and patient care units^{1,2,3}
- Use tall man lettering, a distinctive combination of uppercase and lowercase letters, to distinguish look-alike and sound-alike medications³
- Include the purpose of the medication on all medication orders^{1,2}
- Provide or ask for both the generic and brand names of drugs for medication orders^{1,2}
- When taking verbal orders, write down the drug order and read back the name of the drug, the dosage ordered, and request correct spelling
- Report any medication errors online through Oasis located under Medical Access/Quality and Patient Safety

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Table 1: Recent Additions to the Look-Alike-Sound-Alike Policy

Drug Name	Confused Drug Name(s)
idarubicin	daunorubicin; doxorubicin
metformin	metronidazole
morphine sulfate ER	morphine sulfate IR
Mucinex [®]	Mucomyst [®]
oxycodone	Oxycontin, [®] oxybutynin

Formulary Update

ECHINOCANDINS

Two new echinocandins, micafungin (Mycamine[®]) and anidulafungin (Eraxis[®]) have recently been FDA approved. Echinocandins should only be used in cases of invasive candidiasis when fluconazole resistance is suspected. The P&T Committee has added micafungin to the Formulary as the preferred echinocandin for suspected/confirmed invasive candidiasis. Micafungin will be therapeutically interchanged when caspofungin or anidulafungin is ordered.

EXENATIDE (BYETTA)

Exenatide is an injectable incretin mimetic that is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes who are taking oral antidiabetic agents but have not achieved adequate glycemic control. Exenatide is a long-acting agonist at the glucagon-like peptide-1 (GLP-1) receptor. Nausea is the most common dose dependent side effect. Slow dose titration is essential to minimize adverse effects. The P&T Committee has added exenatide to the Formulary for inpatients and outpatients at Columbus Regional.