Apixaban (Eliquis®): A New Oral Anticoagulant for Atrial Fibrillation

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Clinical Practice Guideline – Update Acute Bacterial Sinusitis in Children

The American Academy of Pediatrics Clinical Practice Guideline on the Diagnosis and Management of Acute Bacterial Sinusitis in Children Aged 1 to 18 years was published on June 24th, 2013. This is the first guideline update since 2001.

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HMG-CoA reductase inhibitors are known as “statins”. As statins are such commonly prescribed drugs, it is crucial to know major interactions and adverse effects associated with them. Statin use carries an increased risk of toxicity when taken with CYP3A4 inhibitors.

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Recently, the FDA added a new Boxed Warning to Pfizer’s antibacterial drug Tygacil, or tigecycline. Pooled analysis of clinical trials has indicated that the drug is associated with increased mortality risk compared to other drugs used to treat serious infections.

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Thomas Pressley PharmD and Deborah Minor PharmD

INTRODUCTION
The new oral anticoagulants (NOACs) are alternatives to vitamin K antagonists (VKAs) for the prevention of thromboembolism in patients with nonvalvular atrial fibrillation (AF). The NOACs with indications for use in AF include dabigatran (Pradaxa®), rivaroxaban (Xarelto®), and apixaban (Eliquis®). With the addition of these NOACs, practitioners are charged with learning how to prescribe these medications to ensure safe and effective use.
The purpose of this review is to discuss AF, the clotting cascade, and parameters associated with the use of the NOAC, apixaban.

BACKGROUND
AF is the most common arrhythmia. With a population prevalence of 0.4 to 1%, approximately 2.2 million Americans have AF. The prevalence increases with age, affecting approximately 8% of individuals aged 80 and older. AF significantly increases the risk of ischemic stroke by four to five-fold. Overall 15% of strokes, and up to 30% in those over 80 years, are attributable to AF. Based on the level of thromboembolic risk, anticoagulation is recommended for many individuals with AF to prevent stroke and systemic embolism.

In AF, disorganized atrial contraction can facilitate the stagnation of blood in the left atrium, increasing the risk of thrombus development. The effectiveness of naturally occurring anticoagulants is attenuated which can result in the activation of the body’s coagulation cascade. If a thrombus develops, the embolus can cause occlusion and precipitate an event. The coagulation cascade consists of intrinsic and extrinsic pathways which converge forming a common pathway. Once activated, both pathways terminate at the common pathway (factor-Xa, F-Xa), producing thrombin (IIa) and fibrin (Ia) to form a stable clot. A number of medications have been developed for the purpose of targeting the various clotting factors and preventing thromboembolic events. Warfarin, the most commonly used VKA, inhibits clotting factors II, VII, IX, and X whereas the NOACs inhibit either Xa or IIa. Because these medications inhibit clotting, the risk of significant bleeding increases with their use.

APIXABAN
Apixaban is an oral, selective, direct F-Xa inhibitor that has a predictable dose response, quick onset of anticoagulation (1 to 3 hours), and a short half-life (~12 hours). Apixaban is indicated for the prevention of stroke and systemic embolism in patients with nonvalvular AF at a dose of 5 mg twice daily. A lower dose of 2.5 mg twice daily is recommended for patients with at least 2 of the following: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine (SCr) ≥ 1.5 mg/dL. Major bleeding and clinically relevant nonmajor bleeding were the most common adverse effects associated with apixaban in trials (2.13% and 2.08%, respectively). Because apixaban has a short half-life, the risk of thromboembolism is increased in patients who are noncompliant with the dosing schedule.

A black box warning highlights the increased rate of stroke observed following discontinuation of apixaban in clinical trials. Therefore, apixaban discontinuation (if anticoagulation remains indicated) for any reason other than bleeding requires treatment with another anticoagulant to decrease the risk of thromboembolism.

Clinical Trials
The clinical trials AVERROES and ARISTOTLE support the use of apixaban in AF. The AVERROES trial randomized 5,600 patients deemed unsuitable for warfarin to apixaban 5 mg twice daily or aspirin 81-324 mg daily (dose selected by local investigator). With a mean follow up of 1.1 years, the trial was terminated early due to the clear benefit of apixaban in decreasing the annual rate of systemic embolism and stroke (1.6% vs. 3.7%; hazard ration [HR] 0.47, confidence interval [CI] 0.32-0.62, p < 0.001). The rates of major
bleeding were similar between the groups (1.4% vs. 1.2%; HR 1.13, CI 0.74-1.75, p = 0.57). The lack of standardization of the aspirin dosing was a subsequent area of criticism.  

The ARISTOTLE trial compared stroke or systemic embolism incidence in 18,201 patients with nonvalvular AF and at least one stroke risk factor (age ≥ 75 years, previous stroke, transient ischemic attack (TIA), or systemic embolism, symptomatic heart failure or left ventricular ejection fraction ≤ 40%, diabetes mellitus, or hypertension requiring pharmacologic treatment). For this population, the mean CHADS₂ score was 2.1 signifying moderate stroke risk. Patients were randomized to apixaban 5 mg twice daily or warfarin titrated to an INR of 2 to 3 (time in therapeutic range = 62.2%). Apixaban was superior to warfarin in annualized rates of stroke or systemic embolism (1.27% vs. 1.60%; HR 0.79, CI 0.66-0.95, p < 0.001, inferiority and p = 0.01, superiority), noninferior in major bleeding (2.13% vs. 3.09%; HR 0.69, CI 0.60-0.80, p < 0.001) and death from any cause (3.52% vs. 3.94%; HR 0.89, CI 0.80-0.99, p = 0.047). The rate of hemorrhagic stroke and ischemic stroke was 49% and 8% lower with apixaban, respectively (p < 0.001; p = 0.42). Intracranial bleeding was significantly less with apixaban (0.33% vs. 0.80%, HR 0.42, CI 0.30-0.58, p <0.001).  

Apixaban has also been studied for VTE treatment and prophylaxis, secondary prevention after ACS, and VTE prevention in metastatic cancer, but indications for these conditions have not been approved.

**Measuring Anticoagulant Effects**

There is currently no acceptable measurement for correlating apixaban’s plasma concentrations with risk of thromboembolism or bleeding. F-Xa inhibitors exhibit varying effects on the prothrombin time (PT) and the activated partial thromboplastin time (aPTT). Because of weak prolongation of the aPTT, variability of assays, and a paradoxical response at low drug concentrations, aPTT is not a useful parameter. Apixaban and other F-Xa inhibitors produce concentration-dependent PT prolongation. However, the effect on the PT depends on the particular F-Xa inhibitor and the assay used to measure the drug’s concentration. Assays sensitivities are reagent dependent and require calibration. Currently there are no specific calibrators for apixaban, but PT may be useful in measuring the anticoagulant effect of F-Xa inhibitors in the future. The international normalized ratio (INR) is unreliable for the evaluation of F-Xa inhibitory activity.

Anti-Xa chromogenic assays have been developed to assess plasma concentrations of F-Xa inhibitors using validated calibrators. These assays are commercially available, but there is currently no data that associate drug plasma concentrations with the risk of bleeding or thromboembolism.

**Drug Interactions**

Apixaban is a substrate of P-glycoprotein (P-gp) and is partly metabolized by CYP3A4. Strong inhibitors of CYP3A4 and P-gp (e.g. azole antifungals, macrolide antibiotics, protease inhibitors) can increase exposure to apixaban and should be avoided if possible. If these medications are necessary, apixaban should be avoided or the dose decreased by 50%. Inhibition of CYP3A4 can result in decreased metabolism of apixaban, whereas P-gp inhibition can increase gut absorption and decrease renal elimination, both resulting in
increased apixaban plasma concentrations and potential risk of bleeding. Strong inducers of CYP3A4 and P-gp (e.g. phenytoin, rifampin) can decrease apixaban’s effectiveness and concurrent therapy should generally be avoided. There are no food interactions with apixaban, and administration can be with or without food.\textsuperscript{5}

Pharmacodynamic interactions occur when apixaban is coadministered with other medications that influence coagulation (e.g. other anticoagulants, platelet inhibitors, non-steroidal anti-inflammatory drugs). The risk versus benefit of combining these medications must be assessed in each situation.\textsuperscript{5,15}

**Switching Between Anticoagulants**

VKA (warfarin) to apixaban: Start apixaban when the INR is < 2.0. If the INR is 2.0-2.5, apixaban may be started the next day.\textsuperscript{5,15}

Apixaban to VKA (warfarin): Apixaban can affect the INR, so measurements during coadministration with warfarin may not be useful in determining the appropriate warfarin dose. It may be necessary to start warfarin and a parenteral anticoagulant (e.g. heparins, fondaparinux) when the next dose of apixaban is due, and discontinue the parenteral anticoagulant when the INR is stable and therapeutic.\textsuperscript{15}

Apixaban to other anticoagulants (e.g. heparins): Discontinue apixaban and start the other anticoagulant at the time of the next scheduled dose.\textsuperscript{5,15}

Parenteral anticoagulant to apixaban: Apixaban can be started once unfractionated heparin (UFH) has been discontinued or when the next scheduled dose of low molecular weight heparin (LMWH) or fondaparinux (Arixtra\textsuperscript{®}) is due.\textsuperscript{5,15}

Apixaban to NOAC or vice versa: The alternative anticoagulant can be started when the next dose of apixaban is due, except when elevated plasma concentrations are suspected (e.g. impaired renal function with dabigatran) in which a longer interval may be necessary.\textsuperscript{15}

**Management of Bleeding**

Unlike warfarin or heparins, the NOACs have no established antidotes for reversal. As a result, management of individuals with bleeding complications related to the NOACs is difficult and based on expert opinion.\textsuperscript{5,15} *In vitro* studies using human blood from healthy donors verified that prothrombin complex concentrates (PCC), activated prothrombin complex concentrates (aPCC), and activated recombinant factor VII (rFVIIa) were effective at reversing apixaban’s anticoagulant effects. PCC and aPCC were more efficient than rFVIIa at reversing apixaban’s effects. However, rFVIIa was the first to produce a blood clot and was more effective in studies with blood circulating through a damaged blood vessel. The authors note that more studies will have to be completed before these therapies can be recommended for apixaban or another F-Xa inhibitor reversal.\textsuperscript{16} Dialysis is not a practical option for the management of bleeding with F-Xa inhibitors because all are smaller molecules and highly protein bound (~87%).\textsuperscript{30} Table 1 highlights suggestions for management of bleeding with F-Xa inhibitors.
<table>
<thead>
<tr>
<th>Severity of bleeding</th>
<th>F-Xa inhibitors (Apixaban)</th>
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<tbody>
<tr>
<td>Non-life threatening</td>
<td>Determine last intake</td>
</tr>
<tr>
<td></td>
<td>Restore homeostasis (12-24 hours)(^a)</td>
</tr>
<tr>
<td></td>
<td>Discontinue medications that prolong anticoagulant effects</td>
</tr>
<tr>
<td></td>
<td>Fluid replacement (colloids if needed)</td>
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<tr>
<td></td>
<td>RBC substitution (if needed)</td>
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<td></td>
<td>Platelet substitution (if needed)</td>
</tr>
<tr>
<td></td>
<td>Fresh frozen plasma as expander (not for reversal)</td>
</tr>
<tr>
<td></td>
<td>Consider desmopressin (coagulopathy or thrombopathy)(^bd)</td>
</tr>
<tr>
<td></td>
<td>Consider tranexamic acid/ aminocaproic acid(^cd)</td>
</tr>
<tr>
<td>Life threatening</td>
<td>All of the above, consider other options including:</td>
</tr>
<tr>
<td></td>
<td>PCC (Kcentra(^®)) 25-50 units/kg (max: 5000 units/dose)</td>
</tr>
<tr>
<td></td>
<td>(repeat dosing not recommended)</td>
</tr>
<tr>
<td></td>
<td>PCC (Bebulin(^®)) 25-90 units/kg every 24 hours</td>
</tr>
<tr>
<td></td>
<td>(repeat dosing may be necessary for 2-3 days)</td>
</tr>
<tr>
<td></td>
<td>aPCC (Feiba(^®)) 50 units/kg (max: 200 units/kg/day)(^e)</td>
</tr>
<tr>
<td></td>
<td>rFVIIa (Novoseven(^®)) 90 mcg/kg(^f)</td>
</tr>
</tbody>
</table>

\(^a\) Apixaban t\(^1/2\) = ~12 h, may be ~24 hours until anticoagulant effects subside

\(^b\) Promotes release of von Willebrand factor promoting coagulation

\(^c\) Antifibrinolytic – inhibits activation of plasminogen to plasmin (responsible for degradation of fibrin)

\(^d\) Very little clinical data to support use in NOAC-associated bleeding

\(^e\) No strong data to support additional benefit over PCC. Can use if PCC not available.

\(^f\) No data supporting additional benefit (only animal evidence). May carry highest risk of thromboembolism following administration

**Special Populations**

**Hepatic impairment:** Because a majority of the dose is hepatically metabolized, apixaban is not recommended in patients with severe hepatic impairment (Child-Pugh C). Patients with mild hepatic impairment (Child-Pugh A) can use apixaban with no dosage adjustment, but caution is advised. Moderate hepatic impairment (Child-Pugh B) suggests some intrinsic coagulation abnormalities but little data is available regarding apixaban’s use in these patients. Therefore, a dosage recommendation is not provided and caution is advised.\(^5\)

**Renal Impairment:** Renal excretion accounts for ~27% of the total clearance of apixaban. Patients with a SCr ≥ 1.5 mg/dL may require a lower dose of apixaban (2.5 mg twice daily) especially if they also have a body weight ≤ 60 kg or age ≥ 80 years. Apixaban is not recommended for use in patients utilizing dialysis or those with a CrCl ≤ 15 mL/min. Currently, no data describes the effect of chronic kidney disease (CKD) on the estimated half-life of apixaban.\(^15\) VKA therapy may be a more suitable alternative to apixaban for patients receiving hemodialysis, with a CrCl ≤ 15 mL/min, or any stage of CKD. VKA therapy management in CKD patients may be influenced by decreased drug elimination, numerous possible drug interactions, and malnutrition. If a NOAC is used in CKD, renal function should be accessed periodically (e.g. every 6 months).\(^5,15\)
**Elderly:** Because elderly individuals are more likely to have some degree of renal insufficiency, the dose of apixaban should be decreased in patients ≥ 80 years (and either SCr ≥ 1.5 mg/dL or weight ≤ 60 kg). In the ARISTOTLE trial, 69% and 31% of individuals were aged ≥ 65 and ≥ 75, respectively. The benefits of risk reduction of stroke and systemic embolism and occurrence of major bleeding with apixaban were maintained in these individuals when compared to warfarin.⁵

**Pregnant or Nursing Mothers:** Apixaban is pregnancy category B and should only be used if the benefits of stroke risk reduction outweigh the risk of hemorrhage during the pregnancy, labor, or delivery. Because apixaban is a relatively small molecule it may be capable of crossing the placenta possibly resulting in fetal adverse effects. Currently, it is unknown whether apixaban or its metabolites are excreted into the breast milk of nursing mothers.⁵ Women may either be instructed to discontinue breastfeeding if apixaban therapy is necessary or to discontinue apixaban in preference to another anticoagulant (e.g. LMWH).⁵,¹⁵

**Race/ethnicity:** No dosage adjustment of apixaban is required based on race/ethnicity. In healthy individuals, results of pharmacokinetic studies showed no differences in apixaban’s pharmacokinetics among Caucasians, Asians, or African Americans.⁵

**Anticoagulation Pre- and Post-Procedure**

Patient characteristics, such as kidney function, age, history of bleeding complications, concomitant medication use, and surgical factors should be considered when deciding how and when to discontinue and restart a NOAC before and after an intervention. Bridging anticoagulation, as with VKAs, is not necessary because the NOACs generally have predictable waning of anticoagulation effects. Depending on the level of bleeding risk associated with a procedure, apixaban may need to be stopped 24-48 hours before the procedure (see Table 2). Surgeries that have a high risk of bleeding complications (e.g. lumbar puncture, liver/kidney biopsy, spinal/epidural anesthesia) may require apixaban discontinuation for at least 48 hours before the procedure.⁵ Even though apixaban prolongs the PT, normalization before an intervention has not been validated.⁵,¹⁵

<table>
<thead>
<tr>
<th>Table 2: Last Intake of Drug Before Elective Surgery¹⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Function</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>No important bleeding risk and/or adequate local homeostasis possible after procedure, perform procedure at trough level of drug (i.e. ≥ 12 or 24 hours after last dose)</td>
</tr>
<tr>
<td>CrCl ≥ 30 mL/min</td>
</tr>
<tr>
<td>CrCl 15 – 30 mL/min</td>
</tr>
<tr>
<td>CrCl ≤ 15 mL/min</td>
</tr>
</tbody>
</table>

Apixaban can be restarted 6 to 8 hours after a procedure that allows an immediate and complete return to homeostasis. Some surgical interventions may carry a bleeding risk that outweighs the risk of embolus formation if full dose anticoagulation is started within the first 48-72 hours after the procedure. Therefore, it is important to weight the risk benefit ratio of bleeding versus thromboembolus formation. It is also important to remember there is no
antidote for reversal of anticoagulation for the NOACs in the case that re-intervention is required. Because they have agents approved for anticoagulation reversal, UFH or LMWH may be best option following a procedure until homeostasis is attained. Once homeostasis is achieved, a NOAC can be substituted for the heparin based therapy, if desired.\textsuperscript{15}

CONCLUSION
The use of warfarin has clearly improved clinical outcomes for many patients with AF. With the introduction of NOACs, advantages and disadvantages of each anticoagulant should be considered when choosing an agent. Selection of an anticoagulant remains highly patient specific, considering patient characteristics, risk of adverse effects, dosing compliance, previous anticoagulant use, and cost. Apixaban and other NOACs are quickly establishing their place in therapy as new data is gained. The NOACs have uniform dosing schedules, require no routine anticoagulation monitoring, and often have fewer drug interactions. However, their lack of clear antidotes and long-term safety data require consideration. Further research is needed for the NOACs to solidify their role in AF management. Regardless of the agent used, appropriate patient education is essential to ensure both medication efficacy and avoidance of adverse effects at all stages of treatment.

REFERENCES
Clinical Practice Guideline – Update
Acute Bacterial Sinusitis in Children

Tara Warren, PharmD

The American Academy of Pediatrics Clinical Practice Guideline on the Diagnosis and Management of Acute Bacterial Sinusitis in Children Aged 1 to 18 years was published on June 24th, 2013. This is the first guideline update since 2001. Acute bacterial sinusitis (ABS) is defined as an inflammation of the paranasal sinuses lasting up to 4 weeks. ABS is commonly preceded by a viral upper respiratory infection (URI) or allergic inflammation.

Major Changes from the 2001 guideline

- Addition of a clinical presentation designated as “worsening course”
- Option to treat immediately OR observe children with persistent symptoms for 3 days
- Imaging is not recommended to distinguish acute bacterial sinusitis from viral upper respiratory infection

Diagnosis

A viral URI can often be confused for an acute bacterial sinusitis. Only 2-10% of all acute sinusitis cases are due to a bacterial infection. Viral infections often differentiate from bacterial
in that they result in steady daily improvements. A diagnosis of acute bacterial sinusitis is recommended if a patient presents with any of the following:

- Persistent illness (nasal discharge and/or daytime cough lasting more than 10 days without improvement)
- A worsening course (worsening or new onset of nasal discharge, daytime cough, or fever after initial improvement, usually on day 6 or 7 of infection)
- Severe onset (concurrent fever \[\text{temperature} \geq 39{\text{°C}}/102.2{\text{°F}}\] and purulent nasal discharge for at least 3 consecutive days)

**Microbiology**

*Streptococcal pneumonia* (*S. pneumonia*) and *Haemophilus influenzae* (*H. influenza*) are each responsible for approximately 30% of cases of acute bacterial sinusitis in children, and *Moraxella catarrhalis* (*M. catarrhalis*) is responsible for approximately 10%. The other 30% of cases are estimated to be sterile. *Staphylococcus aureus* and respiratory anaerobes are both uncommon pathogens for bacterial sinusitis.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Cases of Acute Bacterial Sinusitis</th>
<th>Resistance Mechanism to Amoxicillin</th>
<th>Percentage of Isolates Resistant to Amoxicillin</th>
<th>Mechanisms to Overcome Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. pneumoniae</em></td>
<td>30%</td>
<td>Alteration of the penicillin binding proteins</td>
<td>15 – 50%</td>
<td>Susceptible: MIC \leq2 mcg/mL Intermediate: MIC 4 mcg/mL Resistant: MIC \geq 8 mcg/mL</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>30%</td>
<td>(-)lactamase production</td>
<td>~20 - 50%</td>
<td></td>
</tr>
<tr>
<td><em>M. catarrhalis</em></td>
<td>10%</td>
<td>(-)lactamase production</td>
<td>90-100%</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment**

The American Academy of Pediatrics (AAP) recommends amoxicillin first-line at a standard dose of 45 mg/kg/day in 2 divided doses. Amoxicillin is recommended alone or in combination with clavulanate at a dose of 6.4 mg/kg/day, as that is the minimum amount needed to protect amoxicillin from \(-\)lactamase. The Infectious Disease Society of America (IDSA) differs from AAP by recommending empiric therapy specifically with amoxicillin-clavulanate rather than amoxicillin alone. Both guidelines recommend the option of “watch and wait” as a first-line management in patients that present with a persistent illness and have no risk factors for resistance. AAP’s risk factors for resistance include attendance at child care, treatment with an antimicrobial within the previous 30 days, and age younger...
than 2 years. In communities with a high prevalence of non-susceptible *S. pneumonia*, treatment with amoxicillin may be initiated at 80 to 90 mg/kg/day in 2 divided doses, with a maximum of 2 g per dose. If a patient has any risk factors or is considered to have a moderate to severe illness, they may be initiated with high-dose amoxicillin with 6.4 mg/kg/day of clavulanate. If a child is vomiting, unable to tolerate oral medication, or unlikely to be adherent to the initial doses of antibiotic, ceftriaxone 50 mg/kg/dose may be given intravenously or intramuscularly.

<table>
<thead>
<tr>
<th>Risk for Resistance?</th>
<th>Clinical Presentation</th>
<th>Initial Management</th>
<th>Alternative for Penicillin Allergy</th>
<th>Worse or Lack of Improvement at 72h</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Persistent illness</td>
<td>Watch and wait for 3 days OR amoxicillin +/- clavulanate (45 mg/kg/day, 6.4 mg/kg/day)</td>
<td>Cefdinir, cefuroxime, or cefpodoxime</td>
<td>If initial watch and wait, initiate amoxicillin +/- clavulanate (45 mg/kg/day, 6.4 mg/kg/day) OR high-dose if risk for resistance</td>
</tr>
<tr>
<td>Severe Illness</td>
<td>High-dose amoxicillin-clavulanate (80-90 mg/kg/day, 6.4 mg/kg/day)</td>
<td></td>
<td></td>
<td>Clindamycin + cefixime OR Linezolid + cefixime OR Levofoxacin</td>
</tr>
<tr>
<td>Yes</td>
<td>Persistent, worsening, or severe illness</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a* Attendance at child care, treatment with an antimicrobial within the previous 30 days, and age younger than 2 years.

*b* Does not apply to children with sub-acute or chronic sinusitis.

*c* Observation is not recommended for patients that have orbital or intracranial complications or coexisting illnesses, such as, otitis media, pneumonia, adenitis, or streptococcal pharyngitis.

**Looking Forward**

Due to the approval of pneumococcal 13-valent conjugate vaccine (PCV-13) in 2010, a continuing decrease in isolates of *S. pneumonia* and an increase in β-lactamase–producing *H. influenzae* have been observed. If this trend continues, amoxicillin-clavulanate (45 mg/kg/day) may become the most appropriate empiric treatment option.

**References:**

Increased Toxicity Risk of Statins with Macrolide Use
Ashley Hicks, PharmD Candidate

HMG-CoA reductase inhibitors are known as “statins”. This class of drugs is widely used in dyslipidemia and to prevent further complications of diseases such as diabetes and CAD. The mechanism of the statins inhibits the rate-limiting step of cholesterol synthesis in the liver and mainly targets LDL levels.

As statins are such commonly prescribed drugs, it is crucial to know major interactions and adverse effects associated with them. Statin use carries an increased risk of toxicity when taken with CYP3A4 inhibitors. These toxicities may include rhabdomyolysis, acute kidney injury, or hyperkalemia. Commonly known 3A4 inhibitors are azole antifungals and HIV protease inhibitors. However, the macrolide antibiotics are often overlooked in the interactions with statins. The FDA issued a warning in March 2012 regarding statin use and risks when prescribing the macrolides erythromycin or clairithromycin. Case reports and larger-scale studies alike have reported data validating this warning.

Although erythromycin and clairithromycin are the strongest 3A4 inhibitors of the macrolides, azithromycin has evidence of being a weak 3A4 inhibitor. Thus, azithromycin should not be completely dismissed as a risk factor for a dangerous interaction when taken concomitantly with a statin. Although rare, case reports have shown that azithromycin has caused rhabdomyolysis toxicity in chronic statin users, specifically simvastatin. However, a majority of reports of toxicity have been due to use of erythromycin or clairithromycin.

The HMG-CoA reductase inhibitors atorvastatin, lovastatin, and simvastatin are metabolized by CYP3A4; therefore, these are of the greatest risk for toxicity when administered with CYP3A4 inhibitors.

The prescribing information for most of the statins gives specific recommendations about co-administration with macrolides. A summary of the recommendations is below:
• Rosuvastatin and fluvastatin require no dosage adjustment with macrolides.\textsuperscript{9,10}

• Simvastatin and lovastatin should be discontinued temporarily if erythromycin or clarithromycin therapy is necessary.\textsuperscript{1,8}

• Atorvastatin dose should not exceed 20 mg if prescribed clarithromycin.\textsuperscript{7}

• Pravastatin dose should not exceed 40 mg if prescribed clarithromycin.\textsuperscript{11}

• Pitavastatin dose should not exceed 1 mg if prescribed erythromycin.\textsuperscript{12}

Both statins and macrolide antibiotics are seen frequently prescribed. Attention must be paid to the fact that these two classes of drugs have a major interaction via enzyme CYP3A4. This has the potential to result in the serious adverse events of rhabdomyolysis and myopathies. Preventing this risk will lead to favorable patient outcomes.

References


FDA Drug Safety Update: Tygacil increases risk of death

Linh Huynh, Pharm D. Candidate

Recently, the U.S. Food and Drug Administration (FDA) added a new Boxed Warning to Pfizer’s antibacterial drug Tygacil, or tigecycline. Pooled analysis of clinical trials has indicated that the drug is associated with increased mortality risk compared to other drugs used to treat serious infections. These studies took place following the first warning the FDA issued about Tygacil’s increased risk of death in 2010. According to the studies, patients who took Tygacil for FDA-approved indications had a 2.5 percent risk of death, compared with a 1.8 percent risk of death among those who took other antibacterial drugs. The increased risk was mostly demonstrated in patients treated for hospital-acquired pneumonia, particularly ventilator-associated pneumonia. Patients treated for other types of infections, such as complicated skin and abdominal infections, also had an increased risk of death.¹

The main causes of death included worsening infections, complications from infection or another underlying medical condition. At this time, the reason behind the increased mortality risk has yet to be determined. However, it is suspected that Tygacil may have poor antimicrobial activity due to significant increase in noncure rates compared to other treatments demonstrated by several randomized clinical trials.²

Tygacil is an injectable antibiotic was approved in the United States in 2005. It is indicated for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired bacterial pneumonia. Currently, the FDA recommends that Tygacil should only be used if other treatment alternatives are not feasible.¹ The efficacy of Tygacil in life-threatening infections is only supported by minimal evidence.²
References:


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