Established 2017 Volume 1, Issue 1

ARCH
annual review of changes in healthcare

May 1, 2017

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Annual Review of Changes in Healthcare (ARxCH)

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ARxCH
Annual Review of Changes in Healthcare

Review of Human Immunodeficiency Virus and Updated Guidelines

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Continuing Education Information

CE Hours: 1.00
CEU: 0.100
CE Expiration Date: 5/1/2020
Activity Type: Knowledge
CE Activity # 0449-0000-17-007-H02-P
Please login at https://ufindlaycpe.learningexpressce.com/ and complete the post-test and evaluation to claim your CE credit.

Learning Objectives
- Identify preventative strategies for HIV
- Identify short-term and long-term effects of antiretroviral therapy
- Describe new updates to the guidelines for HIV

Abstract

HIV is a challenging diagnosis for patients with many lifelong implications. It was once a disease state that was associated with a relatively short life expectancy. However, as new drugs have been developed the outcomes have improved drastically. As a healthcare team, it is a duty to keep up with new treatments and therapies that will improve the lives of patients. The HIV/AIDS guidelines are updated regularly, and the most current updated portions are highlighted for easy differentiation. This review will cover some of the updates that occurred in July 2016 and provide a background on the disease state.

Background

Human immunodeficiency virus (HIV) is a viral infectious disease that can be transmitted through multiple body fluids, such as blood, semen, vaginal fluids, and breast milk. HIV can also be transmitted by objects in contact with blood, such as needles. HIV is a retrovirus that attacks the T helper cells and macrophages of the immune system, which help guard against infections and malignancies.[1] Not managed, HIV can cause significant damage to the immune system and transition into acquired immunodeficiency syndrome (AIDS).

The Centers for Disease Control and Prevention (CDC) recommends that persons 13 to 64 years of age get tested for HIV to know his or her status. About 1.2 million individuals in the United States are living with HIV, and it is estimated that one in eight (12.5%) are unaware that they are infected.[2] Men who have sex with men (MSM), African American men, and IV drug abusers are the greatest affected groups in the United States.[2]

Since HIV is not curable, prevention is critical. An important strategy for prevention is awareness of a person's HIV status because knowledge is key. If an individual is HIV positive and desires to remain sexually active, there are options that will provide protection against spreading HIV to his or her partner(s). The individuals involved should use protection, such as a condom or other barrier device. There is also a medication called Truvada® that can be taken for pre-exposure prophylaxis (PrEP) for long-term partners or IV drug abusers, but it should be taken consistently every day.[3] Truvada® is a combination of tenofovir and emtricitabine and can be prescribed to a patient who is at a substantial risk of contracting HIV.[3] When taken properly, the HIV-negative individual has a 92% reduction in risk of being infected.[3] Patients taking Truvada® for PrEP should follow-up with their healthcare provider every three months.[3]

Post-exposure prophylaxis (PEP) is also available for patients. If a patient is involved in a high-risk event, antiretroviral drugs can be administered within 72 hours and can be effective at preventing infection.[4] The therapy is continued for 28 days and must be taken as directed to be effective in preventing HIV.[4]

Transmission

Illicit drug use is a challenge in the treatment of HIV infection. In the United States, the use of injection drugs accounts for the second most common mode of transmission.[5] Regardless if the illicit drug involves a needle, the risk for transmission is elevated. Common reasons for drug use include depression or anxiety, self-treatment of withdrawals, or recreational use.[5] Drug use poses a significant risk of transmission of the HIV virus and co-infection of other viruses because there is a potential of sharing contaminated needles. Additionally, there is an increased incidence for high-risk sexual behavior in this population, especially MSM.[5] It is important to be able to recognize the signs of drug abuse and direct the patient on how to receive help for the underlying problem. If the patient is unwilling to seek help for their addiction, providing information on HIV and

counseling the patient on prevention strategies should be considered.

Use of Antiretrovirals

When an individual with HIV is adherent to their medication regimen, antiretroviral therapy is highly effective at preventing HIV transmission and slowing the progression of the infection.[5,6] Before initiation of antiretroviral therapy, the plasma viral load should be measured.[6] After initiation of antiretroviral medication, the plasma viral load should be measured in two to four weeks, and then again four to eight weeks later until the viral load measurement falls below the assay's limit of detection.[6] It takes eight to twenty-four weeks for full viral suppression to be achieved.[6] At that point, the viral load needs to be measured every three to four months to monitor the viral suppression status.[6] Another important lab measurement is the CD4 cell count, which should be measured prior to medication therapy initiation and then three to six months or annually thereafter.[6] The measurement will assess the need for prophylactic treatment of opportunistic infections, which may occur in patients with a more advanced HIV infection who have a severely suppressed immune system (CD4 cell count less than 200). There are several combinations of antiretroviral medications; patients will normally need to use three active drugs from at least two different classes.[6] If the drug regimen is changed, the combination needs to involve at least two active drugs or viral suppression could fail due to viral rebound.[6]

All medical personnel play a crucial role in HIV awareness, prevention, and education. Creating an open and honest relationship with patients about the HIV infection, lifelong medication outcomes, responsibilities, illicit drug use, and preventative care for sexual partners will decrease the risk of transmission.[5]

Complications with the Use of Antiretrovirals

It is important to assess a patient's awareness and readiness to begin therapy.[5] Initiating antiretroviral therapy in a patient that may not be adherent to the regimen may create resistant strains of the virus. Patients can experience a wide array of side-effects from antiretroviral medications. Some of the immediate effects include CNS-effects, such as abnormal dreams, dizziness, headache, and depression, skin rash, and gastrointestinal side-effects.[5,6] For some patients, the side-effects have a negative impact on adherence. Therefore, this is an important counseling point. Creating an open dialogue about medication complications and adherence at every visit may improve outcomes.[5] Long-term adverse effects of antiretroviral medication use can be cardiovascular disease, diabetes mellitus/insulin resistance, bone density effects, dyslipidemia, severe hepatotoxicity, lactic acidosis, lipodystrophy, myopathy, psychiatric effects, renal effects and CKD, and severe hypersensitivity reactions, including Stevens-Johnson syndrome.[6]

Other long term effects of antiretroviral therapy can be seen in renal and liver function. An institution-based retrospective study (n=275) was conducted in Ethiopia from 2010 to 2015 to look at long-term antiretroviral effects on the kidney and liver.[7] The included participants needed to have been taking antiretroviral

drugs for at least three years, registered for primary care at the University of Gondar Hospital ART clinic, and screened for renal and liver dysfunction prior to initiation of therapy.[7] This study found that the overall prevalence of CKD increased after treatment with antiretrovirals, and a majority of the CKD cases after treatment were in stage 3 of CKD.[7] Other studies have shown a higher prevalence of patients with stage 2 CKD after treatment with an antiretroviral.[7] In addition to the increased prevalence in CKD, the study by Biadgo, et al. showed that forty-six of the participants had a presence of hepatotoxicity after treatment with an antiretroviral.[7]

Knowledge Check: Possible immediate adverse effects of antiretroviral medications include:

a) Headache
b) GI side-effects
c) Skin rash
d) Dizziness
e) Abnormal dreams
f) Three of the above
g) All of the above

Answer: G

HIV Guideline Update

HIV therapy guidelines are updated regularly. The Panel members involved in the HIV guideline committee have monthly teleconferences in which they discuss modifications and updates to the most recent guidelines.[6] There is at least one representative on the Panel from the U.S. Department of Health and Human Services (HHS), Centers for Disease Control and Prevention (CDC), U.S. Food and Drug Administration (FDA), Health Resources and Services Administration (HRSA), and National Institutes of Health (NIH), which consists of about forty-five elected members with expertise in HIV care and research.[6]

In July of 2016, the guidelines were updated. The key updates to the guidelines were for HIV-infected women, tuberculosis (TB)/HIV coinfection, combination regimens for antiretroviral-naive patients, regimen switching, Hepatitis B Virus (HBV)/HIV coinfection, and Hepatitis C Virus (HCV)/HIV coinfection.[6]

For all HIV-infected women, the Panel emphasized recommending antiretroviral therapy (ART).[6] This strong recommendation is evidenced by one or more randomized trials with clinical outcomes. Expert opinion strongly recommends that if a woman is not planning on getting pregnant that she should take an oral contraceptive.[6] If the antiretroviral (ARV) drug regimen has a significant interaction with hormonal contraceptives, then it is appropriate to use alternative or additional contraceptives.[6] Switching to a different ARV drug is an option, however, it is only moderately backed by expert opinion.[6] If an HIV-infected woman does become pregnant and was not on an ARV combination, it is necessary to discuss the risks and benefits of ARV use during and after pregnancy. The updated guidelines increase the amount of counseling that should be done with HIV-infected women.[6] Expert opinion strongly suggests initiating

ART as soon as possible to prevent mother-to-child transmission (MTCT) of HIV.[6]

The Panel recommended an update on the treatment of latent tuberculosis infection (LTBI) because the treatment of LTBI reduces the risk of active TB in HIV-infected patients.[6] Guidelines suggest that any ART regimen can be used if the patient is taking isoniazid alone for LTBI treatment.[6] If the patient is receiving once-weekly isoniazid plus rifapentine for LTBI, then expert opinion strongly suggests an efavirenz (EFV) or raltegravir (RAL)-based ART regimen.[6] The once weekly isoniazid (INH) and rifapentine regimen is given for twelve weeks.[6] The CDC also recommends either isoniazid daily or twice weekly for nine months or rifampin daily for four months.[6] In all patients with active TB who are not on therapy, an antiretroviral should be initiated.[6] The addition to the guidelines pertains to patients with CD4 counts of at least 50 cells/mm.[3,6] The TEMPRANO randomized study consisted of 2,056 HIV-infected patients who did not meet the WHO criteria for ART initiation.[6] There were four study arms. One arm deferred ART initiation. The second arm deferred ART plus INH preventative therapy (IPT). The third arm initiated early ART, and the fourth arm initiated early ART plus IPT. For patients with CD4 counts greater than 500 cells/mm^3, the early initiation of ART immediately had positive effects by reducing the risk of death and HIV-related illness by 44 percent.[6] Six months of IPT reduced the risk of HIV morbidity by 35 percent.[6] Expert opinion strongly suggests initiating ART within eight weeks of initiating TB treatment.[6] The PREVENT TB study showed that there was no significant difference in safety and effectiveness of preventing active TB between rifapentine plus INH for twelve weeks compared to nine months of INH alone in patients who were not on ART.[6] An important drug interaction to consider is with rifamycins, which are important in TB treatment.[6] The drugs in the class pose a variety of interactions.[6] Tenofovir alafenamide (TAF) is a P-gp substrate and is impacted by concomitant administration of rifamycin.[6] Due to this drug-drug interaction, administration of both TAF and rifamycin is not recommended.[6]

Based on observational studies, the Panel recommends to use a combination of tenofovir disoproxil fumarate (TDF) with emtricitabine (FTC) or lamivudine (3TC) or use tenofovir alafenamide and emtricitabine (TAF/FTC) as the nucleoside reverse transcriptase inhibitor (NRTI) backbone of the ARV drug regimen for patients coinfected with HIV and HBV (hepatitis B virus).[6] The update includes recommendations on the potential use and restrictions of TAF/FTC-containing regimens.[6] TAF/FTC-containing regimens are not recommended to be used in patients with a creatinine clearance less than 30 ml/min.[6] Switching to elvitegravir/cobicistat/tenofovir/alafenamide/emtricitabine (EVG/c/TAF/FTC) can reduce renal and bone toxicity while effectively suppressing HBV.[6] Adefovir is associated with a high incidence of renal disease, and telbivudine is associated with myopathy, HBV treatment failure, and neuropathy. Therefore, the Panel is currently not recommending adefovir and telbivudine for HBV/HIV-coinfected patients.[6]

Conclusion

Overall, there were many important updates to the guidelines for HIV in July 2016. Women of reproductive age that are infected with HIV and are not planning on becoming pregnant, should consider taking an oral contraceptive and ART.[6] Women who are pregnant should weigh the risks and benefits of using ART to reduce the risk of MTCT.[6] The updated guidelines increase the amount of counseling that should be done with HIV-infected women. HIV/TB co-infected patients have better outcomes taking ART and TB treatment compared to TB treatment without ART.[6] The Panel recommends a combination of TDF with FTC or 3TC or use TAF/FTC as the NRTI backbone of the ARV drug regimen for HIV patients coinfected with HBV.[6] HIV therapy is going to continue to evolve to try to improve the quality of life for over a million patients in the United States.

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ARxCH
Annual Review of Changes in Healthcare

Summary of 2016 CHEST Guidelines

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Continuing Education Information

CE Hours: 1.00
CEU: 0.100
CE Expiration Date: 5/1/2020
Activity Type: Knowledge
CE Activity # 0449-0000-17-006-H04-P
Please login at https://ufindlaycpe.learningexpressce.com/ and complete the post-test and evaluation to claim your CE credit.

Learning Objectives
•Describe key updates to the 2016 CHEST Guidelines
•Discuss the key evidence behind updated recommendations
•Identify how changes to the guidelines will impact pharmacy practice
•Describe which therapeutic options would be appropriate when given patient data

Abstract

This review highlights the changes in recommended therapy, made by the American College of Chest Physicians in February 2016, for the treatment of venous thromboembolism disease. The data behind these recommendations has been evaluated to provide health care professionals with a more in-depth understanding of the treatment options available for their patients. This review discusses several gaps in the literature for health care professionals to note, as these are areas for further elucidation in the treatment of venous thromboembolism disease.

In February of 2016, the American College of Chest Physicians published an updated version of Antithrombotic Therapy for Venous Thromboembolism (VTE) Disease. With novel anticoagulants on the market, these updated guidelines now more accurately reflect treatment options available and further explain which patient populations can safely and effectively be treated with different agents. Currently, no studies directly compare new oral anticoagulants (NOACs) in regards to safety and efficacy; therefore, the guidelines do not state a preference as to the use of one novel agent over the others.[1] Due to this, NOACs will be listed in alphabetical order throughout this review and do not appear in the order as to which they should be initiated for patient care. Through this review, the updated guideline recommendations will be further discussed.

Several new recommendations were made when considering choice of an agent for long-term anticoagulation therapy, with long term meaning three months of treatment.[1] In patients with deep vein thrombosis (DVT) of the leg or pulmonary embolism (PE) who do not have active cancer, it is suggested to start apixaban, dabigatran, edoxaban, or rivaroxaban over vitamin K antagonists (VKA).[1] For each outcome being assessed, the data from more than 5,000 participants was pooled. The data collected consisted of multiple trials where dabigatran and edoxaban were each compared to VKA, and apixaban and rivaroxaban were individually compared to both VKA and low-molecular weight heparin (LMWH). In the assessment of all-cause mortality, apixaban showed the largest risk reduction when compared to VKA and LMWH (RR=0.82, CI 0.61-1.08, p=0.16).[3] This data was collected from one study, which looked at adults with proximal deep-vein thrombosis, pulmonary embolism or both.[3] In this trial death from any cause was assessed as a secondary composite endpoint.[3] This study was powered at 90%, which indicates that there is a high ability to detect a difference between treatment groups.[3]

Alternatively, edoxaban showed a slight increase in risk when compared to VKA (RR=1.05).[5] This information was gathered from a study that looked at adults with deep vein thrombosis or pulmonary embolism (with or without DVT).[5] This study was powered at 85% giving the researchers a high ability to detect a difference between treatment groups.[5] Death from VTE events, cardiovascular events, cancer, infectious disease, and other was reported in 3.2% of participants treated with edoxban and 3.1% of participants treated with warfarin.[5] A confidence interval or p value were not reported by the authors of this study. However, the updated guidelines report a relative risk of 1.05 (CI 0.82-1.33) showing a 5% increase in the risk of death from any cause with use of edoxaban compared to warfarin.[1] The guidelines conclude this to be about 2 more deaths per 1000 patients treated with edoxaban. [1]

The collected data for recurrent VTE showed that those treated with dabigatran were at an increased risk for recurrent VTE compared to VKA (RR=1.12) while other NOACs showed a decreased risk of recurrent VTE. [1] A trial (RE-COVER) that included adults with DVT or PE who were treated with either dabigatran or warfarin for

6 months found an increased risk of recurrent VTE in patients taking dabigatran compared to those receiving warfarin therapy (RR 0.4, CI -0.8 - 1.5).[2] This trial was powered at 90%, giving it a high ability to detect differences between treatment groups. It is important to note that patients receiving warfarin therapy were within therapeutic range about 60% of the time.[2] Depending on specific patient populations the average amount of time spent in the therapeutic range may differ and could potentially change the results of this outcome. In a second study, adults with DVT or PE who were recruited from the previous study (RE-COVER) or had been receiving anticoagulation therapy with an approved agent were evaluated for efficacy of dabigatran versus warfarin therapy.[6] This study was powered to 85% and found a hazard ratio of 1.44 (CI 0.78-2.64, non-inferiority p=0.01) when determining efficacy of dabigatran versus warfarin for prevention of recurrent VTE.[6] In patients receiving warfarin therapy, the INR was found to be within the therapeutic range about 65% of time during the duration of this trial.

Apixaban, dabigatran, edoxaban, and rivaroxaban have shown decreased risks of major bleeding compared to VKA.[1] The choice of which anticoagulant to initiate should be influenced by patient-specific factors. Therapy with VKA is recommended over NOACs for patients with renal disease or poor compliance. [1] VKA or apixaban is recommended in patients with dyspepsia or a history of GI bleeding. [1] For patients with coronary artery disease the recommended agents include; VKA, apixaban, edoxaban, and rivaroxaban. [1] If once daily dosing is preferred then options include VKA, edoxaban, and rivaroxaban.[1] If parenteral therapy should be avoided then options for anticoagulants include apixaban and rivaroxaban.[1]

In patients with DVT of the leg or PE who also have active cancer, low molecular weight heparin should be utilized for anticoagulation therapy over VKA therapy, apixaban, dabigatran, edoxaban, or rivaroxaban for long term therapy.[7,8] Further research is still required to support safe and effective use of new anticoagulants in patients with active cancer. [1]

Nine studies were evaluated to determine the risk of all-cause mortality, recurrent VTE, and major bleeding events between LMWH and VKA therapy. A risk reduction of 0.65 (CI 0.52-0.83) was found from the pooled data in regards to recurrent VTE for LMWH.[1] This shows that patients treated with LMWH had a significantly lower risk of experiencing an additional VTE event. In regards to major bleeding, treatment with LMWH was found to be associated with a lower risk when compared with VKA (RR 0.86, CI 0.56-1.32). [1]

A revision to the wording of one recommendation was made in the CHEST guideline update: When considering extended anticoagulant therapy, or lifelong treatment, patients may continue treatment with the agent initiated for long-term therapy.[1] The authors wanted to clarify that there is not a need to change agents for anticoagulation therapy once the decision has been made to continue treatment from long-term to extended therapy. However, if there have been changes to the patient's health or preferences since beginning long-

term therapy then a different anticoagulant may be considered.

Aspirin may be considered for extended treatment in patients who have experienced unprovoked proximal DVT or PE and have decided to stop treatment with anticoagulants.[1] Before initiating therapy with aspirin, verify that the patient does not have any contraindications to aspirin use. In a study designed to evaluate aspirin use and the risk of recurrent VTE in patients previously treated with VKA agent for 3 months (WARFASA), a hazard ratio of 0.58 (CI 0.36-0.93, p = 0.02) was found, which shows a lower risk for recurrent VTE in patients treated with aspirin than with no anticoagulation therapy.[9] In another study (ASPIRE), adults with their first episode of unprovoked DVT or PE were studied. This study was powered at 80%, and the study was not able to recruit enough study participants to achieve this power, so the sample size from this study was combined with the results from the WARFASA study in order to reach a power of 80%. With the pooled analysis, aspirin showed a hazard ratio of 0.74 (CI 0.52-1.05, p = 0.09) showing a non-significant decreased development of subsequent episodes of VTE in patients taking aspirin versus placebo.[10] This recommendation may help provide protection against VTE events in patients who are continuing their anticoagulation therapy.

Several updates to the guidelines were included to specifically address patient populations who have experienced a pulmonary embolism (PE); these updates include the following: In patients with subsegmental PE and no proximal DVT of the legs, the risk of recurrence determines choice of therapy.[1] If there is a low risk of recurrent venous thromboembolism (VTE), clinical surveillance is recommended over anticoagulation therapy.[1] In patients with a high risk of recurrent VTE, anticoagulation therapy should be initiated.[1] The authors of the CHEST guidelines consider the following to be risk factors for recurrent or progressive VTE; hospitalization, reduced mobility, active cancer, low cardiopulmonary reserve, symptoms not attributed to another condition, and no reversible risk factors like recent surgery.[1] There is a low quality of evidence behind this recommendation as no randomized trials were identified that have assessed patients with subsegmental PE.[1] In its place, trials that examined patients with larger PEs were assessed under the assumption that the results may similarly apply to patients with subsegmental PE.[1] Out of 60 reported cases of subsegmental PE who were not treated with anticoagulants, there were no reports of recurrent DVT or PE at a three-month follow up.[11] All 60 patients underwent compression ultrasonography and half were found to have an underlying asymptomatic DVT.[11] This suggests that the risk of recurrent VTE for a patient if left untreated with anticoagulation therapy is low. However, due to the small sample size involved in this study there is still uncertainty surrounding the actual risk of no anticoagulation therapy in patients with subsegmental VTE. A second study analyzed data from two prospective outcome studies that evaluated patients suspected of having a PE.[12] In both outcome studies, patients found to have a PE were treated with heparin or low molecular weight heparin, and a VKA for 6 months.[12] A total

of 3769 patients were evaluated, results showed that there was no significant difference between patients with subsegmental PE and patients with segmental or proximal PE in regards to recurrent VTE (HR 1.6, CI 0.5-4.8). [12] Clinical differences between groups include higher rates of malignancy, immobility, recent surgery, and estrogen use in patients with subsegmental PE.[12] The results of this study offer an alternative viewpoint as to the clinical significance of subsegmental PEs, suggesting that subsegmental PEs may be treated similarly to more proximal PEs.

Another updated recommendation for patients with pulmonary embolisms is in patients with a low-risk PE, treatment at home or early discharge can be considered over standard discharge if patient-specific factors allow.[1] The suggested criteria that should guide the decision whether to treat at home or in the hospital includes: clinically stable with good cardiopulmonary reserve; no contraindications such as recent bleeding, severe renal or liver disease, or severe thrombocytopenia; expected to be compliant with treatment; the patient feels well enough to be treated at home. [1] In one meta-analysis, the risk of recurrent VTE was evaluated from pooled results of 13 studies assessing patients who were either treated outpatient, treated inpatient for whole length of treatment, or treated inpatient and discharged early (within three days). Results of this analysis found a risk of recurrence in patients treated in an outpatient setting to be 1.7% (CI 0.92-3.1), patients discharged early had a risk of recurrence of 1.1% (CI 0.22-5.43), and patients treated inpatient had a risk of recurrence of 1.2% (0.16-8.14).[13] These results suggest similar risks of recurrence despite different treatment settings. In a systematic review that included eight studies, the risk of recurrent VTE was evaluated. Rates of recurrence between the eight studies were reported to range from 0-6.2%. [14] It is also important to note, seven of the eight studies were prospective cohort studies, offering a lower quality of evidence.

Another updated recommendation specifically addressing patients with PE is: For patients with acute PE and no hypotension, no systemic thrombolytic therapy is recommended.[1] In this population who also have a low bleeding risk and deteriorate after anticoagulant therapy is initiated, systemic thrombolytic therapy is recommended.[1] Patient deterioration is defined as development of a progressive increase in heart rate, decrease in systolic BP, increased jugular venous pressure, worsening gas exchange, signs of shock, right heart dysfunction, or increased cardiac biomarkers.[1] In a meta-analysis, 15 studies were included that were randomized controlled trials comparing use of an intravenous thrombolytic agent and heparin versus heparin alone for treatment of acute PE (I_2 0%).[14] The pooled results found a significant reduction in early mortality associated with use of a thrombolytic agent (OR 0.59, CI 0.36-0.96, p 0.03); however, results were not significant when patients with high-risk PE (an acute PE with sustained systemic arterial hypotension) were excluded. [14] This is important to as note as the guidelines recommend no thrombolytic therapy in patients with a PE without hypotension. Additionally, a randomized controlled trial evaluated heparin and tenecteplase (a thrombolytic

agent) versus heparin alone in patients with right ventricular dysfunction and myocardial injury. In this study, patients treated with tenecteplase were at a lower risk of death and hemodynamic decompensation (OR 0.44, CI 0.23-0.87, p = 0.02).[15] These results suggest that the use of thrombolytic therapy in patients with signs of decompensating may be beneficial.

If treated with a thrombolytic agent, systemic thrombolytic therapy using a peripheral vein is recommended over catheter directed thrombolysis (CDT).[1] There are currently no randomized or observational studies comparing CDT with systemic thrombolytic therapy.[1] In a randomized controlled trial, patients with diagnosed PE were assigned to receive unfractionated heparin and either intravenous or intrapulmonary thrombolytic agent (1 or 2 doses depending on severity of embolism). [15] The results of this study found the number of patients that required a second dose of thrombolytic agent was not significantly different between the two treatment groups. Results also found no significant difference, after the first dose of thrombolytic agent, in the following areas; pulse rate, respiration rate, mean pulmonary arterial pressure, pulmonary 02 saturation, and pulmonary angiographic score.[16]

Specific recommendations addressing patients who experienced recurrent VTE while on anticoagulation therapy are made: If using VKA therapy, apixaban, dabigatran, edoxaban, or rivaroxaban for anticoagulation therapy, it is suggested to switch to LMWH and if the patient was using LMWH for anticoagulation therapy, it is suggested to increase the dose by one-quarter to one-third.[1] The quality of evidence surrounding these recommendations is of low quality as there are no randomized trials or prospective cohort studies that address the management of patients with recurrent VTE while on anticoagulation therapy. The authors of the CHEST guidelines suggest six points to be considered when determining the next course of action.[1] It is also noted that the reason for recurrence should guide what changes are to take place in the patient's anticoagulation therapy. The recommendation in the guidelines to increase the dose of LMWH if this agent was being used while recurrent VTE occurred is supported by a retrospective observational study which found that cancer patients with recurrent VTE who switched from VKA to LMWH or who increased their dose of LMWH by about 25% resulted in both acceptable risk of recurrence and major bleeding events.[17] After experiencing a recurrent VTE while on anticoagulant therapy, evidence suggests that increasing intensity of therapy can be accomplished by switching from an oral agent to an injectable agent (such as low molecular weight heparin) or by increasing the dose of low molecular weight heparin. [17]

Another observation in the updated guidelines states the routine use of compression stockings is not recommended to prevent post-thrombotic syndrome (PTS). This recommendation is based on the findings of a large, multi-centered, placebo-controlled trial, which did not find significant benefit to routine use of graduated compression stockings for prevention of post thrombotic syndrome or for reduction of leg pain during the three months after DVT diagnosis.[18] A total of

806 patients were evaluated in this trial, 14.2% of those with compression stockings and 12.7% of those without compression stockings experienced PTS (HR 1.13, CI 0.73-1.76, p = 0.58).[18] The results of this trial conflict with previous practice and no longer suggest that patients wear compression stockings for prevention of PTS. This change in care benefits patients as they no longer need to spend money for a treatment that is not beneficial to their care. This also alleviates the need to be compliant with a treatment option that may create discomfort for the patient.

Knowledge Check: True or False? Compression stockings should be recommended for prevention of post-thrombotic syndrome

Answer: False

Changes to the recommendations for management of VTE should be put into practice immediately to provide patients with the most effective treatments available. Of note, the guidelines have also placed an emphasis on patient preference and patient specific factors when appropriate. This partially may be due to a lack of knowledge regarding new oral anticoagulation options and their niche in therapy. The guidelines identified several areas where there is a gap in research. These areas include; head to head comparisons of NOACs, use of NOACs in patients with active cancer, treatment for recurrent VTE in a patient currently on a NOAC, and randomized controlled trials of patients with subsegmental PE. This demonstrates the significance in assessing the data that supports each recommendation. One may choose to watch the literature for new studies that fill the knowledge gap in order to provide a higher level of care for their patients. As further research is conducted, guideline recommendations may change or, alternatively, may be supported by a stronger level of evidence.

Overall, changes to the CHEST guidelines for treatment of VTE provide an important impact on patient care as they offer more effective treatments through either the addition of new options in anticoagulation or through the deletion of ineffective treatments.

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Annual Review of Changes in Healthcare

Entresto: An Overview for Pharmacists

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Continuing Education Information

CE Hours: 1.00
CEU: 0.100
CE Expiration Date: 5/1/2020
Activity Type: Knowledge
CE Activity # 0449-0000-17-005-H04-P
Please login at https://ufindlaycpe.learningexpressce.com/ and complete the post-test and evaluation to claim your CE credit.

Learning Objectives
•To inform pharmacists of a new agent used in the treatment of NYHA class II-IV heart failure
•To inform pharmacists of clinical trial results supporting efficacy and safety of Entresto
•To inform pharmacists of alternative/combination target sites/mechanisms of Entresto
•To inform pharmacists of common adverse effects associated with Entresto

Abstract

Entresto is a new drug that was developed for NYHA stage II heart failure. It was evaluated through the PARAMOUNT-HF and PARADIGM trials and showed some benefits to patients suffering from heart failure. There are many products that are approved for the treatment of heart failure to either decrease morbidity/mortality or provide symptom relief. It is a serious disease state and provides pharmacists with an opportunity to make appropriate recommendations in order to benefit patients. This review will discuss different characteristics of Entresto and some of the evidence associated with its use.

Not only do 5.7 million people in the United States have heart failure, but one in nine deaths in 2009 were from heart failure.[1] Roughly half of all people who are diagnosed with heart failure die within five years.[1] Heart failure is also associated with a total national cost of approximately $30.7 billion.[1] Coronary heart disease, hypertension, and diabetes are the most common comorbidities that predispose a person to developing heart failure.[1] This disease state is a serious issue facing the United States, and it is imperative that work be done to combat this condition.

Heart failure is defined by the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) as impairment in the ability of the heart to eject blood or perform ventricular filling.[2] This damage may be in the endocardium, pericardium, heart valves, or other anatomical areas. Typical signs and symptoms result from peripheral edema and pulmonary congestion which leads to dyspnea and fatigue. The New York Heart Association (NYHA) defines stages of heart failure based on physical activity. Stage I indicates there is no limit on physical activity, whereas stages II, III, and IV specify slight limitation, marked limitation or the inability to engage in any physical activity without severe symptoms, respectively. Pharmacotherapy has historically targeted the renin-angiotensin-aldosterone system when treating heart failure. Other heart failure treatments include diuretics and beta-antagonists.[2]

Angiotensin Converting Enzyme (ACE) inhibitor therapy has been the foundation of heart failure treatment due to the significant decreased risk of death shown in clinical studies.[3] Angiotensin receptor blockers (ARBs) have typically been reserved for patients who suffered from adverse side effects or in patients who could not tolerate ACE inhibitors. Entresto (sacubitril/valsartan) contains a new product called sacubitril which acts as a neprilysin inhibitor in addition to valsartan (an ARB). Neprilysin is an enzyme responsible for the degradation of several endogenous vasoactive peptides including natriuretic peptides and bradykinin. Eliminating the degradation of these endogenous vasoactive peptides ultimately results in increased vasodilation, natriuresis, and diuresis. Valsartan blocks the binding of angiotensin II to AT1 receptors. Ultimately this blocks the vasoconstrictive and aldosterone stimulating effects of angiotensin II.[5]

Entresto is primarily indicated for use in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction to reduce the risk of cardiovascular death and hospitalization.[2] Entresto should always be administered in conjunction with other heart failure therapies and in place of other ACE/ARB therapies.[2]

Pregnant women should avoid Entresto as it is a known teratogen. The black box warning states that this drug may cause fetal abnormalities and therefore, it is necessary to counsel women of child-bearing age about this important risk. Lactating women are advised not to take Entresto as it was found in animal trials to be secreted in breast milk. It is also important to inform patients prescribed Entresto to report side effects including: signs/symptoms of kidney dysfunction (urinary retention, blood in urine, change in amount of urine passed, or weight gain),

signs/symptoms of high potassium (abnormal heartbeat, confusion, dizziness, passing out, weakness, shortness of breath, numbness or tingling feeling), loss of strength and energy, angioedema, or dry hacking cough.[5]

Dosage strengths (sacubitril/valsartan respectively) vary from 24/26mg, 49/51mg, and 97/103mg and are referred to as 50mg, 100mg, and 200mg respectively.[4] The recommended dose to titrate to is the 97/103mg strength. Entresto is not recommended in severe liver impairment, and renal adjustments need to be made when estimated glomerular filtration rate (eGFR) is reduced to less than 30 mL/min.[5] Patients who are currently taking an ACE-inhibitor should not be started on Entresto until 36 hours after their last dose (washout period).[2]

Knowledge Check:
Entresto therapy aims to replace which of the following current HF therapies?

A) ACE/ARB therapy in NYHA class II-IV HF patients
B) ACE/ARB therapy in all HF patients (NYHA class I-IV)
C) ACE/ARB therapy ONLY in severe HF cases (NYHA class IV)
D) None of the above

Answer: A

The PARADIGM-HF trial was a prospective comparison of Angiotensin–Neprilysin Inhibition compared to an ACE inhibitor (enalapril) to determine the impact on global morbidity and mortality in heart failure. This study was designed to provide evidence to support the replacement of ACE inhibitors or ARBs with Entresto in the management of chronic heart failure.[6] In this trial, the primary outcome was a composite of death from cardiovascular causes or first hospitalization for heart failure.[6] Over eight thousand patients with NYHA class II-IV symptoms with EF ≤40% were included (4187 patients were randomly assigned to Entresto treatment, and 4212 received enalapril for the intention-to-treat analysis).[6] Death from cardiovascular causes or hospitalization for heart failure occurred in 914 patients (21.8%) in the Entresto group and 1117 patients (26.5%) in the enalapril group (hazard ratio in the Entresto group = 0.80; 95% confidence interval [CI], 0.73 to 0.87; P<0.001).[6] The study concluded that Entresto was superior to ACE inhibition alone and prevented one or more cardiovascular deaths or heart failure hospital admissions for every 21 patients treated for two years when compared to enalapril.[6] The study stated that the superiority of Entresto over enalapril was not accompanied by important safety concerns and that fewer patients stopped their study medication in the Entresto group than in the enalapril group because of an adverse reaction.[6]

A second trial called the PARAMOUNT study was a prospective comparison trial. PARAMOUNT was a phase II randomized, parallel grouped, double blind, multicenter trial that observed patients with NYHA heart failure preserved ejection fraction (HFpEF) of 45% or higher and pro-brain naturieretic peptide (pro-BNP)

greater than 400 pg/mL.[7] Elderly females were a majority of the study participants with about one quarter of them having atrial fibrillation as a comorbidity. Roughly half of all patients in the trial had diabetes and some form of kidney dysfunction.[7] Patients received Entresto (titrated to a strength of 200mg) twice daily or valsartan (160 mg) twice daily for 36 weeks. Pro-BNP is a peptide marker of heart failure and therefore was a primary outcome. This peptide marker was significantly reduced at 12 weeks in the Entresto group compared with the valsartan group. The Entresto group's pro-BNP dropped by 178 pg/ml and the valsartan group's pro-BNP dropped by 27 pg/ml on average. Adverse drug events were notably similar amongst groups taking Entresto and those taking only valsartan.[7]

Based on these studies, Entresto has shown to be an important drug for the future and appears to be an asset in the treatment of heart failure as a replacement to traditional ACE/ARB therapy. According to the PARAMOUNT and PARADIGM trials, patients who take Entresto may have better health outcomes on average versus those who do not. Pharmacist involvement in patients with heart failure is an important aspect of care for these patients in the future. A focus on the relevance of these trials and proper recommendations to providers may help patients in the United States with heart failure achieve better outcomes.

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The Rising Incidence of *C. difficile* and Bezlotoxumab: The Targeting of Toxin B

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Abstract

Clostridium difficile (*C. difficile*) infection has become a growing issue facing hospitals in North America and Europe. Each case of *C. difficile* infection is now being shown to add $7,200 to the cost of a patient's stay. These growing incidents and costs have spurred research in new treatments of this infection. Metronidazole and oral vancomycin continue to be the preferred first-line drugs with the macrocyclic agent, fidaxomicin, a possible option for some patients. From a more procedural route, fecal microbiota transplants are seeing an increase in use due to their high success rate.

Bezlotoxumab (Zinplava), a monoclonal antibody approaches *C. difficile* treatment from a different angle. When used with a *C. difficile* targeting antibiotic, bezlotoxumab binds to Toxin B, a sizable and destructive toxin released by the *C. difficile* bacterium. By binding to this toxin, bezlotoxumab gives the gastrointestinal mucosa time to heal and time for the normal flora to grow. Bezlotoxumab is not a replacement for antibiotics.

The MODIFY I and MODIFY II trials were the largest conducted trials to date for *C. difficile* treatment. These trials studied nearly 2,700 patients worldwide and compared bezlotoxumab to placebo and actoxumab, a monoclonal antibody that instead targeted Toxin A. Actoxumab was found to be ineffective, however, the completion of both trials showed bezlotoxumab to be superior to placebo and to significantly reduce the *C. difficile* recurrence rates (p=0.0003).

Since murumonab-CD3 was approved for use in 1986, monoclonal antibodies have become preferred drugs for a wide variety of disease states. Orthoclone OKT3 (muromonab-CD3) was approved for the prevention of kidney transplant rejection through its targeting of the antigen CD-3. While side effects and advancements in transplant therapy have caused its withdrawal from the United States market, it is considered a landmark in antibody therapy and was the impetus to a new age of medicine.[1]

Monoclonal antibodies have been shown to effectively treat several forms of cancer, Alzheimer's disease and numerous autoimmune diseases such as ulcerative colitis, rheumatoid arthritis and Crohn's disease. Debilitating and incurable diseases have become manageable through breakthroughs that are becoming increasingly common. The next target for monoclonal antibodies? Infections.[1]

Clostridium difficile (*C. difficile*) is the leading cause of hospital-acquired diarrhea in North America and Europe.[2] Recent antibiotic exposure and gastric acid suppressants (PPIs/H2RAs) have been shown to predispose patients to a greater risk of contracting this infection.[2] This antibiotic-associated diarrhea emerges through a competition mechanism of *C. difficile* versus the depleted normal GI flora.[3] However, patients once thought to be at low-risk are being infected at increasing rates as the spread of this bacterium continues. It is estimated that each case of *C. difficile* increases hospital costs by $7,200, amounting to more than $5 billion in the United States each year.[4] The CDC has noted a 20-fold increase in mortality, resulting in 29,000 deaths in 2011.[2]

C. difficile is spread through an oral-fecal route and is non-invasive in nature, however, it is most lethal because of two toxins that are released: toxin A (TcdA) and toxin B (TcdB).[5,6] These two toxins, each about 300 kilodaltons (kDa), are two of the largest bacterial toxins known. It is speculated that of the two toxins, TcdB poses the chief threat as it is estimated to cause ten times greater damage to epithelial tissue of the colon than toxin TcdA.[6,7] Once this epithelial barrier is disrupted, this toxin begins to target and break down underlying cells, colonocytes, enterocytes and enteric neurons.[5] This breakdown of epithelial tissue can lead to bloating, hematochezia, toxic megacolon, colon perforation, sepsis and eventually death if not properly treated.[5]

Aptly named because of its difficulty to treat and eradicate, *C. difficile* is resistant to most antibiotics. Discontinuation of the causative antibiotic is widely recommended as necessary for effective treatment. However, the real challenge is preventing and effectively treating recurrent infections. Repeat regimens of metronidazole and/or vancomycin are recommended and vancomycin may be administered as a tapered regimen at some point.[8] Current guidelines according to the American College of Gastroenterology for the treatment of *C. difficile* infection recommend metronidazole (500mg TID for 10 days) for patients with mild to moderate cases and vancomycin (125 mg QID for 10 days) for patients with severe or complicated cases.[8] Fidaxomicin 200 mg daily for 10 days is also an option for treating recurrent infections.[9]

In the last five years, increasing virulence and incidence has led to a need for additional options to prevent recurrences. Fidaxomicin is a narrow-spectrum macrocyclic antibiotic which selectively targets *C. difficile* while preserving the normal GI flora.[10] While vancomycin has shown to be equally effective to fidaxomicin in the first treatment, the difference in recurrence rate showed fidaxomicin to have a statistically significant edge in preventing recurrence in patients not infected with the hypervirulent strain. Although it is quite expensive, at a cost of $3,360 for a 10-day treatment compared to $700 for vancomycin capsules, $25 for oral vancomycin compounded from intravenous vancomycin and $35 for metronidazole, its clinical application can be effective in patients with unbearable, chronic *C. difficile* infection.[11] Fecal microbiota transplant is another form of alternative therapy that is growing in usage. Fecal donors free of infectious diseases such as HIV, hepatitis C and other qualifications provide a stool sample that is mixed with saline and then placed into a patient through the route of colonoscopy, nasogastric tube or enema.[12] Fecal transplants have demonstrated great success in preventing recurrence of *C. difficile* infection with cure rates as high as 91%.[12] The ingestion or infusion of bacteria from a healthy donor passes through the GI system and competes with the *C. difficile* bacteria for resources, therefore restoring the normal gut flora of the patient.[12]

Bezlotoxumab (Zinplava) approaches *C. difficile* treatment from a different angle. One of the first drugs of its kind, bezlotoxumab is a monoclonal antibody that binds to the receptor binding domain of toxin B which prevents Toxin B from binding to human cells.[13] Bezlotoxumab is not indicated for the treatment of *C. difficile* infection by itself.[14] Patients must be on standard antibiotic therapy of vancomycin/metronidazole to treat the infection and then are given one intravenous infusion of bezlotoxumab 10mg/kg over 60 minutes.[15] When a patient is prescribed vancomycin or metronidazole, the gut flora of good and bad microbes may be wiped out. After antimicrobial therapy, patients are at their highest risk of recurrence of infection caused by the remaining toxins in the GI tract.

Bezlotoxumab crosses the gut wall to the site of infection via toxin-mediated disruption of the epithelium.[13] Bezlotoxumab provides passive immunity towards toxin B produced by persistent or newly acquired *C. difficile* bacterium.[13] This allows the body's normal microbiota to recolonize the gut once antibiotics have been stopped.[13] The growth of normal bacteria in the body will reestablish the body's normal check against *C. difficile* growth by ways of competition for nutrients thus lowering the risk of recurrent infection. However, bezlotoxumab is not to be used in place of antibiotic therapy.[13]

In a study conducted by Merck, bezlotoxumab was evaluated on its own and in combination with another Merck monoclonal antibody, actoxumab. Actoxumab differs from bezlotoxumab in that it targets the less harmful toxin TcdA.

Bezlotoxumab was studied in two main phase 3 trials named Modify I and II. These are the largest *C. difficile* treatment trials to date and assessed nearly 2,700 patients across 300 sites, 30 countries and

six continents.[13] The Modify I trial contained four arms for comparison: bezlotoxumab, actoxumab, both together and then placebo; the Modify II trial contained three arms in bezlotoxumab, both bezlotoxumab and actoxumab together, and placebo. Patients were randomly assigned oral vancomycin, metronidazole or fidaxomicin treatment and then randomly stratified into one arm of the trial.[13] Four hundred patients were studied in each arm of each trial, leading to 1,600 patients for Modify I and 1,200 patients for Modify II. Actoxumab alone was discontinued in the second trial due to minimal efficacy in the treatment of recurrence.[16] Each trial contained a power of 95% or higher. The completion of both trials showed bezlotoxumab to be superior to placebo and to significantly reduce the *C. difficile* recurrence rates (p=0.0003).[13] This came to a 10% absolute risk reduction and a relative risk reduction of 40% of *C. difficile* recurrence for each trial.[13] From this the number needed to treat with bezlotoxumab to prevent a recurrence of infection was ten patients. In addition, actoxumab did not show a difference in recurrence rates when combined with bezlotoxumab.[13]

Bezlotoxumab has a half-life of about 19 days and is eliminated mostly by protein catabolism.[13] There is no hepatic metabolism nor renal elimination.[13] Because of the process by which bezlotoxumab is eliminated, organ dysfunction and age are not anticipated to affect the exposure of bezlotoxumab.[13] However, the clearance of bezlotoxumab has shown to increase in patients with greater body weight.[13] No other dose adjustment factor was seen during clinical trials including demographically different patients, elderly patients, patients with multiple disease states, hepatic impairment, or renal impairment.[13] Bezlotoxumab has low potential to be involved in a drug interaction with another drug.[13] As with many monoclonal antibodies, side effects and cost are concerns. When bezlotoxumab is given with standard of care antibacterial drugs for *C. difficile,* the most common adverse effects seen in clinical trials include nausea, pyrexia, and headache.[15] There is no established information regarding the safety or efficacy of bezlotoxumab in pregnant women, lactating women, or pediatric use. A more serious side effect that became apparent in the Modify trials was the potential for worsening of heart failure.[15] Patients with a history of congestive heart failure are more susceptible to this risk and should only take bezlotoxumab if the benefit outweighs this risk.[15]

The recent approval of bezlotoxumab has the potential to have a large impact on the standard treatment of *C. difficile* infection. Recurrent *C. difficile* infection has been greatly associated with normal treatment and has continually been a problem, but until high costs of monoclonal antibodies begin to decrease, bezlotoxumab can be reserved as an effective therapy for patients in dire need of an end to recurrent *C. difficile* infection.[7] Bezlotoxumab treatment in combination with standard of care medication can reduce the rate of recurrent infection and in turn decrease the length of hospital stays and hospital readmittance. Reducing the length of hospital stays and readmissions can help improve the quality of care for patients.

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Review of Parkinson's Disease Treatment and Future Therapies

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Abstract

Parkinson's Disease (PD) is a progressive neurodegenerative disorder that can affect an individual's ability to perform daily activities. The disease belongs to a group of motor system disorders and is characterized by the result of a loss of dopamine-producing brain cells. There are no definitive causes of this condition, but there are many factors currently being studied. Genetics, environmental factors, or a combination of both may be potential causes of the disease. This article will review current treatment regimens used in practice, previous studies done on novel therapies, and future therapies that could have clinical significance.

The review will go through each medication class and highlight their mechanisms, potential side effects, and use in the treatment of Parkinson's disease. Clinical trials researching newly approved medications are referenced in the article. Areas of future drug development that are being studied are also reviewed. New information is constantly being discovered regarding the pathophysiology of Parkinson's Disease, which in turn leads researchers to look into new potential therapies.

Background

Parkinson's Disease (PD) is a progressive neurodegenerative disorder that can affect an individual's ability to perform daily activities. The disease belongs to a group of motor system disorders and is characterized by the result of a loss of dopamine-producing brain cells. PD is estimated to affect 0.3% of the United States' population, and 4-5% of individuals 85 years old or older.[1] It is most commonly seen in people over the age of 60. Currently there are no blood or laboratory exams that have been able to help with the specific diagnosis of PD. The disorder is difficult to diagnose accurately, as the diagnosis is based on medical history and a neurological examination.

There are no definitive causes of this condition, but there are many factors currently being studied. Genetics, environmental factors, or a combination of both may be potential causes of the disease.[2] A mutation in the gene called LRRK2 is estimated to be the most common genetic mutation that triggers PD.[3,4] This defect is more frequent in individuals of North American descent.[3] Mutations in the protein alpha-synuclein have also been found to trigger PD, but these are quite rare and this protein is being studied extensively.[3] Exposure to pesticides, certain heavy metals and repeated head injuries can increase the risk of developing PD.[3] Many individuals that have developed Parkinson's do not have a clear environmental cause, as the connection is often difficult to establish.[3] Environmental causes like insecticides, herbicides, and head injuries are just a few potential causes. Sadly, there is presently no cure for Parkinson's Disease, but there are an assortment of medications that have been shown to provide a dramatic relief from the symptoms.

Dopamine is a neurotransmitter that is released by the brain that has a large variety of roles in different functions in the body that include: memory, behavior, attention, pleasurable reward, and most importantly for Parkinson's – movement.[2] PD is caused from dopamine cell loss in the substantia nigra. This chemical imbalance is responsible for the manifestation of the symptoms.[2] The importance of dopamine is why many treatment goals of PD are to increase the levels of dopamine in the brain.

Symptoms

Symptoms of Parkinson's Disease vary greatly from individual to individual, both in terms of intensity and progress. PD symptoms are classified into two categories: motor and non-motor. Observing the motor symptoms of PD is the main way physicians diagnose PD.[5] These motor symptoms include: tremor, rigidity, bradykinesia, postural instability, and walking/gait difficulties.[5] Tremor will characteristically occur at rest, and is a classic slow, rhythmic tremor usually starting in one hand, foot, or leg before progressively affecting both sides of the body. Rigidity can be wrongly attributed to arthritis or orthopedic problems. The slow movement of PD is commonly demonstrated by a reduced or mask-like expression of the face, a decreased blink rate of the eyes, and problems with fine motor coordination. Vocal symptoms are common in individuals

with PD. The individual's voice may become softer, or start off strong and then fade away. There are many non-motor symptoms that are common in patients with PD. These include: decreased sense of smell, inability to stay asleep, depression, anxiety, fatigue, cognitive changes, weight loss, drooling, and gastrointestinal issues.[5] Early detection of all of these symptoms is important for the patient's overall health and quality of life so treatment can begin as soon as possible.

Treatment

Treatment of Parkinson's Disease is broken down into two categories: early-stage and late-stage. Early-stage PD usually includes patients who have had the disorder for less than 5 years or have not developed motor complications from levodopa use.[6] Late-stage PD is described as patients who have received carbidopa/levodopa for at least five years and have developed motor complications.[6] Motor complications, such as the wearing-off phenomenon and dyskinesias, develop with increasing frequency in patients after 5-6 years of dopaminergic therapy.[6] About half of elderly individuals with PD experience dyskinesias and almost 100% of younger patients under the age of 40 experience dyskinesias after 6 years of levodopa therapy.[6]

Levodopa is the most common and most effective agent for the treatment of Parkinson's Disease.[6] It is the primary treatment for symptomatic patients in both early and late stages.[6] Levodopa is usually combined with carbidopa in a combination medication called Sinemet. Carbidopa is needed to prevent peripheral conversion of levodopa to dopamine by blocking dopa decarboxylase. This allows levodopa to cross the blood-brain barrier and be converted into dopamine without being broken down in the plasma.[6] This medication is most effective in controlling bradykinesia and rigidity.[7] Some side effects of Sinemet include nausea/vomiting, confusion, orthostatic hypotension and hallucinations.[7] Levodopa/Carbidopa has been shown to be very effective in the treatment of PD, yet long-term treatment with this medication has been shown to be associated with motor fluctuations and dyskinesias.[6] Individuals being treated with Sinemet commonly suffer from the "On-Off Phenomenon", which is a very important challenge in the long-term treatment of PD. After receiving levodopa for 5-10 years, at least 50% of PD patients develop motor complications that are a major cause of disability in advanced PD.[6] Evidence suggests that these motor complications are associated with non-physiological, pulsatile stimulation of dopamine receptors.[6] During the "On-Phase", the patient has improved mobility as they are responding well to the levodopa therapy. The patient will then fluctuate to the "Off-Phase", where they will develop impaired motor functions as the levodopa therapy wears-off. The changes are rapid, severe, and frequent, which makes this phenomenon very unique. Smaller, more frequent doses, or larger, less frequent doses, may be more effective in some patients.[6] A decrease in dietary protein or the use of bromocriptine and selegiline may be helpful, but only for temporary improvement.[6] Subcutaneous Apomorphine, controlled-release formulations of levodopa with a peripheral dopa-decarboxylase

inhibitor, and continuous intra-duodenal administration of levodopa are also options in the management of the "On-Off Phenomenon".[8]

Dopamine agonists are a common medication in the treatment of Parkinson's Disease. These medications directly stimulate the dopamine receptors. Bromocriptine (Parlodel), pergolide (Permax), pramipexole (Mirapex), and ropinirole (Requip) are medications in this class. This class of medications have been shown to be effective as monotherapy, or combined with levodopa, in the treatment of PD during the early stages of the disease.[6,7] Dopamine agonists are commonly one of the first anti-parkinson's medication used in newly diagnosed patients. Side effects include: impulse control disorders, sedation, dizziness, fatigue, hypotension, weakness, and increased risk of infection.[7]

Monoamine oxidase B (MAO-B) inhibitors irreversibly and selectively inhibit brain MAO-B, which reduces the breakdown of dopamine.[7] Monoamine oxidase B causes the breakdown of dopamine. Medications in this class are: selegiline (Eldepryl) and rasagiline (Azilect). These medications are effective in symptomatic control of PD.[7] The benefits are usually mild to moderate. MAO-B inhibitors are also useful as adjuvant therapy for patients with PD and motor fluctuations. Side effects include orthostatic hypotension, dyskinesias, falls, depression, headaches, and dyspepsia.[7] It is important to use caution with the concomitant use of cyclobenzaprine, dextromethorphan, methadone, propoxyphene, St. John's Wort or tramadol.[7] The MAO-B inhibitors will increase the concentrations of these medications.

Catechol-O-methyltransferase (COMT) inhibitors will reversibly and selectively inhibit COMT, which blocks COMT conversion of dopamine in the gut and periphery. This will help prolong the half-life of levodopa/carbidopa and the AUC, which allows for a decrease in the daily levodopa dose. The two COMT-inhibitors are: entacapone (Comtan) and tolcapone (Tasmar). Side effects include: diarrhea, liver failure, and exacerbation of levodopa adverse effects.[7]

Another PD medication, Amantadine (Symmetrel), is a NMDA-receptor inhibitor. This medication has a somewhat debated mechanism, but it seems to increase dopamine release from the striatum by stimulating dopamine receptors. It will also reduce dopamine uptake along with inhibiting NMDA receptors. Amantadine is useful for treating akinesia, rigidity, tremor, and dyskinesia.[7] Some side effects include nausea, hallucinations, insomnia, confusion, depression, and orthostatic hypotension.[7] It is important not to discontinue this medication abruptly, as it could lead to an increase in dyskinesia. A decreased dose is needed in renally impaired patients. Patients with a creatinine clearance between 30-50ml/min will have to take 200 mg on day 1 and decrease their dose to 100 mg daily from day 2 on. With a CrCl of 15-29ml/min, patients will have to take 100mg on alternate days after the initial 200mg dose. Lastly, if a patient has a CrCl <15ml/min or are on hemodialysis, they will need to be administered 200mg every 7 days.[7]

In the last 15 years, there have been many studies suggesting the effectiveness of

deep brain stimulation (DBS) in the treatment of PD. The best results have been reported in patients who have had advanced PD with at least five years of disease duration, positive response to levodopa therapy, relatively younger age for PD, low axial non-levodopa responsive motor symptoms, very mild or lack of cognitive impairment and absence of or well-controlled psychiatric disease.[9] With these criteria, a very small percentage of patients suffering from PD may be eligible for DBS treatment.

Previous Studies

With Parkinson's Disease having an unknown cure as well as a significant prevalence, many clinical trials are being done on new treatment options for the disease. Studies exploring the potential of Coenzyme Q10 (CoQ10) in the treatment of PD have been published. In 2014, a randomized clinical trial was published on the effects of high-dosage Coenzyme Q10 in early PD.[10] 600 participants were randomly assigned to receive placebo, 1200 mg/d, or 2400 mg/d of CoQ10 and all participants also received 1200 IU/d of vitamin E.[10] Even though the Coenzyme Q10 was well tolerated and shown to be safe in this population, there was no evidence of clinical benefit.[10]

Another clinical trial in 2014 investigated the safety, tolerability, and urate-elevating capability of the urate precursor inosine in early PD.[11] Urate is an antioxidant that researchers believe may have the potential for being effective in PD treatment. The antioxidant showed neuroprotection against oxidative stress-induced dopaminergic neuron death in rodent models of PD.[11] The trial showed that inosine was generally safe, tolerable, and effective in raising serum and cerebrospinal fluid urate levels in early PD. More studies in humans need to be developed to support inosine as a potential disease-modifying therapy for PD.

Many patients suffering from Parkinson's disease may experience delusion and hallucination symptoms during the course of their illness. These symptoms cause decreased quality of life and make treatment more difficult for patients. In April 2016, pimavanserin (Nuplazid) was approved for the treatment of delusions and hallucinations of PD. The medication is a second generation atypical antipsychotic and is a novel 5-HT_{2A} inverse agonist and antagonist. While it reduces activity at serotonin 5-HT_{2A} receptors, it does not block dopamine receptors, which is why it is believed to not worsen Parkinson symptoms while many other antipsychotics do.[12] Some adverse effects of this medication include peripheral edema, confusion, nausea, and urinary tract infections. This medication is very costly ($2,000/month) and is mainly used in a specialty pharmacy environment, so widespread clinical practice use is limited.

Published in April 2017, a randomized trial studied the effectiveness of low-dose rasagiline and pramipexole as a combination agent (P2B001) in early stage Parkinson's Disease.[13] Patients enrolled in the study were randomized into one of three groups: two groups received the combination with one group receiving a higher dose, and the third group received a placebo for 12 weeks. The primary endpoint

of the study was the change from baseline to final visit in Total-UPDRS score versus placebo.[13] 136 patients completed the study and significant benefits were observed for both doses of the combination, P2B001.[13] Nausea and somnolence were more common with P2B001 treatment, yet adverse events were overall comparable to placebo. Pramipexole is FDA-approved as monotherapy for early PD, and with this study showing promising results, the future of early PD treatment could begin to involve more than just dopamine agonists. More studies need to be completed before clinically significant changes occur.

New and Future Therapies

As it was stated previously, many anti-Parkinson's medications are add-on therapies to levodopa to improve motor fluctuations without exacerbating dyskinesia. In March 2017, a new anti-Parkinson's medication, safinamide (Xadago) was FDA-approved.[14] It is an MAO-B inhibitor approved for adjunctive treatment to levodopa/carbidopa in patients with PD experiencing "off" episodes. This medication was studied in clinical trials to assess its effectiveness in patients with motor fluctuations on levodopa therapy. The primary endpoint of the study was total "on" time with no or non-troublesome dyskinesia.[14] Patients enrolled in the study were given 100 mg/day of safinamide, 50 mg/day of safinamide, or placebo for 24 weeks.[14] The study found the addition of safinamide, 50mg or 100mg, to current levodopa therapy in patients with PD and motor fluctuations significantly increased total "on" time with no or non-troublesome dyskinesia.[14] The study also found decreased "off" time, improved parkinsonism, and no significant differences for adverse events between groups.[1,14] With this medication it is important to monitor the patient's liver function, as it is recommended to not be used in severe hepatic impairment.[7,14] The next step for safinamide, now that this medication is approved, would be for studies to compare the effectiveness of safinamide with other MAO-B inhibitors to assess if it is non-inferior or superior to other MAO-B inhibitor agents.

As there is still unknown causes of PD, future therapies are always in development. Intrajejunal constant-rate infusion of levodopa is a fairly new therapeutic option to help provide a constant dopaminergic level in the blood.[6] This will help increase the "on" time for patients by preventing motor fluctuations and intractable dyskinesias of patients with advanced Parkinson's disease. Studies are being conducted to further support and validate this treatment approach as well as look at technical liabilities for long term therapy.[6] Newer molecules are being evaluated for reducing dyskinesias which include: glutamate receptor antagonists, cannabinoid receptor antagonists, a2-adrenergic receptor antagonists, adenosine A2A-receptor antagonists, and 5-HT1A-receptor agonists.

Conclusion

Parkinson's disease is a complex disease that affects more individuals on a daily basis. The current therapeutic options have been shown to be effective in the treatment of Parkinson's. Sadly, these

medications are not as effective after long periods of time due to their side effect profiles and the nature of the disease. New treatment options are constantly being studied to decrease dyskinesias and increase the "on" time for levodopa.

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DOAC Reversal Agents

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Abstract

Direct oral anticoagulant (DOAC) drugs revolutionized the anticoagulant market and pose an attractive alternative approach to the treatment and prevention of VTE, as well as the prevention of stroke in atrial fibrillation (A. Fib) patients. DOAC agents include dabigatran etexilate (PRADAXA), rivaroxaban (XARELTO), apixaban (ELIQUIS), and edoxaban (SAVAYSA). Dabigatran etexilate functions mechanistically as a direct thrombin inhibitor, whereas rivaroxaban, apixaban, and edoxaban are factor Xa inhibitors. These agents are more expensive when compared to warfarin therapy (classic Vitamin K antagonist), but have fewer monitoring demands, fewer food interactions, and may offer a more patient-friendly outpatient dosing regimen.[1] One unique characteristic of DOACs is the ability for DOAC anticoagulation effects to be rapidly reversed. DOAC specific reversal agents (idarucizumab, andexanet alfa, and ciraparantag) have recently become available or are currently undergoing phase 2 and 3 trials. This review article will focus on specific reversal agents and some of their characteristics.

Managing DOAC therapy around invasive procedures involves consideration of the current patient situation. Clinicians should take into consideration the urgency of the procedure and determine whether it is possible to delay invasive operations.[1] For patients who are on a DOAC due to recently having an invasive operation, the risk of recurrent VTE is highest during the first 3 months post operation.[1] For elective procedures, clinicians should first consider whether the procedure can be delayed until a time that the patient may not require a DOAC, or is at least several months after the initial event due to the risk of recurrence.[1] For patients requiring long-term anticoagulation or who cannot delay a procedure, clinicians must assess the risks and benefits of the abrupt therapy interruption. When therapy interruption is necessary, the cessation and resumption of the DOAC around the elective procedure is determined according to bleeding risk, renal function, and DOAC half-life.[1]

As with all anticoagulant drugs, bleeding is a major complication that can develop and cause life threatening hemorrhagic conditions to arise. Where DOACs have previously failed to match warfarin is in the category of rapid reversal, possibly explaining why many prescribers may be partial to warfarin. Vitamin K or fresh frozen plasma infusion have functioned as warfarin reversal agents during episodes of bleeding or hemorrhage, but there has not been a reversal agent for the DOAC agents in the cases when rapid reversal has been needed (traumatic bleeding, emergency surgery, hemorrhage etc).[2] Typically, due to the short half-lives of DOAC agents, relatively abrupt discontinuation of these medications can suffice in eventually reversing their effects.[3] In times of emergency, when discontinuation reversal will not be enough, it is essential that alternative reversal strategies target individual DOAC agents while taking into consideration the urgency of the situation. Thus, several agents have been developed over the last several years to meet this need. These agents will likely be used clinically in patients with life-threatening bleeding such as intracranial hemorrhage and retroperitoneal bleeding, as well as in patients requiring emergency/immediate surgery.[4] This review looks to compare characteristics of DOAC reversal agents, that are both FDA approved as well as currently undergoing phase 2 and 3 studies.

Idarucizumab (Praxbind)

Idarucizumab received FDA approval in October 2015 as a reversal agent that rapidly neutralizes the anticoagulant effect of dabigatran. Idarucizumab is a monoclonal antibody fragment that binds directly to dabigatran with an extremely high affinity.[4] The affinity of idarucizumab for dabigatran is approximately 350-fold stronger than the affinity of dabigatran for thrombin.[4] This allows idarucizumab to be highly specific to dabigatran, prevent binding to other thrombin substrates (factors V, VIII, or XIII, fibrinogen, von Willebrand factor, protease-activated receptor 1, and protein C), as well as having no effect on platelet aggregation.[4] In the Phase III RE-VERSE AD prospective cohort study, 90 patients were divided into two groups.[5]

Group A included patients with uncontrollable/life threatening bleeding that required a reversal agent, and group B patients included those who required an invasive procedure/surgery within the next 8 hours.[5] Patients received 5 g of intravenous idarucizumab, which was administered as two 50-ml bolus infusions, each containing 2.5 g of idarucizumab, no more than 15 minutes apart.[5] The median plasma concentration of unbound dabigatran at baseline was 84 ng/mL in group A and 76 ng/mL in group B.[5] In samples obtained after the first vial of idarucizumab was administered, the concentration of unbound dabigatran was less than 20 ng/mL; a level that produced a negligible anticoagulant effect (in all but one patient).[5] These levels were maintained for roughly 24 hours.[5]

Uses: Dabigatran reversal prior to emergency surgery
Dose: 5 grams IV given in two separate doses of 2.5 grams no more than 15 minutes apart.[6]
Time of onset: "immediately" decreasing the plasma concentrations of dabigatran after IV with complete bleeding cessation in 11.4 hours.[4]
Negative aspects: coagulation correction as soon as 1-4 hours after Praxbind injection; may consider a second dose.[4]
Warnings/Side effects: Patients with known hypersensitivity reactions with idarucizumab or any components of its formulations should be evaluated against the potential benefit of emergency dabigatran reversal.[6] Thromboembolic risk in patients after dabigatran reversal; reinitiate dabigatran 24 hours after idarucizumab reversal.[6]

Andexanet alfa

Andexanet is a recombinant modified human factor Xa decoy protein that retains no enzymatic activity within the human body, but retains the ability to bind factor Xa inhibitors at the active site with high affinity.[7] The efficacy and safety of andexanet alfa on apixaban and rivaroxaban anticoagulation reversal was assessed in the ANNEXA-A and ANNEXA-R trials. Participants in the ANNEXA-A study received apixaban orally where as participants in the ANNEXA-R study received rivaroxaban orally.[7] After achieving max plasma concentration of apixaban, andexanet was administered as an intravenous (IV) bolus or as an IV bolus with or without continuous infusion.[7] After achieving max plasma concentration of rivaroxaban, andexanet was administered as an intravenous bolus or as an equivalent intravenous bolus followed by a continuous infusion.[7]

Anti–factor Xa activity was rapidly reduced and thrombin generation was rapidly restored (within 2 to 5 minutes) to a greater extent after administration of a bolus of andexanet than after administration of placebo, both in the apixaban study and in the rivaroxaban study (p-value <0.001 in both studies).[7] After administration of the andexanet bolus was completed, the reversal of anti–factor Xa activity persisted for 2 hours and thrombin generation increased to above the lower limit of the normal range within 2 to 10 minutes.[7]

The study claimed that there were no serious or severe adverse events, no thrombotic events, as well as no neutralizing antibodies present.[7] Non-neutralizing

antibodies against andexanet were detected in 17% of patients who received andexanet and tended to appear within 15 to 30 days after andexanet administration.[7] Hypersensitivity reactions could be a cause of a severe adverse reaction in future trials. The ongoing ANNEXA-4 phase 3b–4 study is evaluating the efficacy and safety of andexanet in patients with factor Xa inhibitor–associated acute major bleeding.[7] Andexanet alfa received FDA approval for "Breakthrough Therapy" designation in November 2013 and orphan drug status in February 2015. "Breakthrough therapy" designation is similar to a fast track designation.[9] In order to meet this criteria, preliminary clinical evidence must demonstrate that the drug may have substantial improvement on at least one clinically significant endpoint over available therapies.[9]

In conclusion, andexanet adds a specific and rapidly acting antidote that is being developed for urgent reversal of factor Xa inhibitor anticoagulant activity.[7] The ability of andexanet to reverse anticoagulation in participants undergoing anticoagulation therapy with apixaban, rivaroxaban, edoxaban, or enoxaparin makes it a potential widespread antidote for direct and indirect factor Xa inhibitors.[7] The rapid onset and offset of action of andexanet paired with the ability to administer it as a bolus or as a bolus plus an infusion may provide flexibility with regard to the restoration of hemostasis when urgent factor Xa inhibitor reversal is required.[7]

Uses: Rapid acting antidote for direct and indirect factor Xa inhibitor anticoagulant medications

Doses: 400-960mg IV bolus or bolus plus infusion.[7]

Time of Onset: Thrombin generation restored 2-5 minutes after bolus dosing.[7]

Warnings/side effects: In one study, one patient developed hives.[7] No other severe side effects or thrombotic events were reported.

Ciraparantag

Ciraparantag (PER977) is a small, synthetic, water-soluble molecule designed specifically as an IV reversal agent targeting DOACs and heparins.[4] It has been shown to form a complex with larger molecules such as unfractionated heparin and LMWH, as well as with smaller molecules such as fondaparinux, apixaban, edoxaban, rivaroxaban, and dabigatran and inhibits antithrombin interaction.[4] Ciraparantag exhibits no binding to plasma coagulation factors or albumin therefore exhibiting no procoagulant effect.

Ciraparantag was investigated in a double-blind, placebo-controlled, dose-escalation trial involving 80 healthy volunteers.[4] Trial participants were randomly assigned to cohorts to receive single-dose IV ciraparantag 5, 15, 25, 50, 100, 200, or 300 mg or placebo.[4] Study participants received oral edoxaban 60 mg followed by single dose IV ciraparantag or a placebo 3 hours later at edoxaban max concentration.[4] Edoxaban administration increased whole blood clotting time (WBCT) by 37% over the baseline value.[4] Participants receiving ciraparantag 100, 200, or 300 mg expressed a decreased WBCT to within 10 percent above the baseline value in 10 minutes or less, suggesting a full

reversal of anticoagulant effects, and values remained in that window for 24 hours.[4] One recognizable limitation of a universal reversal agent is that it may interfere with the emergency use of an anticoagulant during a procedure for patients requiring heparins for extracorporeal life support or cardiopulmonary bypass support.[2] Research is also required to determine when anticoagulation can be restarted after ciraparantag administration. Ciraparantag received fast-track status from the FDA in April 2015 and is currently undergoing additional phase II trials under Perosphere Inc, with Phase III clinical trials planned for the future.[4,8]

Conclusion

These agents provide a method of anticoagulant reversal for patients who cannot wait for an extended period of time post DOAC discontinuation in order to undergo a procedure. These situations include patients with life-threatening bleeding such as intracranial hemorrhage and retroperitoneal bleeding, as well as in patients requiring emergency/immediate surgery to "safely" undergo surgery without an extensive risk of bleeding.

Clinicians will need to have unmistakable evidence supporting that the patient is truly in immediate need of a rapid anticoagulant reversal agent to justify one being used. The need for these agents in the moment will have to be significant, as these agents will be relatively costly. Clinicians will also have to become familiar with new guidelines and treatment regimens. The ability to rapidly reverse DOAC therapy may positively influence the confident use of them more frequently in the clinical setting. Hospital pharmacies will need to accommodate the storage requirements for these new agents by preparing/maintaining proper refrigeration and inventory management. Hospitals will also have to consider modifying/programming "smart-pump" infusion devices for these agents.

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Review of Iron-Overdose in Pediatric Patients

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Abstract

The occurrence of iron overdose in children remains a prevalent occurrence in the United States despite efforts to combat this issue. This review discusses the mechanism behind iron poisoning, the presentation of toxic effects, and available treatment options after a potential poisoning has occurred. Keeping this information in mind when discussing iron-therapy with patients who have children at home is important. Parents and guardians of children should be made aware to contact poison control, 911, or bring their child to the nearest hospital.

The candy-like appearance of many medications can look desirable to children and have them confused as to the serious implications that may occur after ingestion. Specifically, the appearance of iron supplements has led to many cases of iron poisoning in children as these pills are typically sugarcoated and brightly colored.[1] There is also an assumed low-risk to iron-containing products, such as multivitamins, that may lead to less restricted access to these medications.[1] Iron over-dose is one of the leading causes of death in children under six years old, with approximately seventy-five percent of all iron overdose cases in 2014 being in children younger than six years old.[2] The risk of death from iron overdose in pediatric patients is ranked as high as other agents like cocaine, anticonvulsants, and antidepressants.[3] As health care professionals, it is important to have an awareness of prevalent adverse outcomes in the community. Using this knowledge, key preventative measures can be included along with medication counseling points to help in decreasing overdose situations. When ingested, iron is stored in a protein called ferritin, which is primarily found in tissue of the liver and heart.[4] The mechanisms of iron poisoning come into play after the iron-binding protein, ferritin, becomes saturated.[4] Even after there are no available proteins for binding, iron still is directed to the liver and heart and as a result, damage to these organs is seen early on in an overdose situation.[4] Several mechanisms are suggested as to how excess free iron may cause damage to the body. In the acidic environment of the stomach iron can cause direct irritation.[4] As iron travels through the gastrointestinal tract it becomes insoluble, forming complexes that lead to mucosal damage.[4] Free iron that passes across the cellular membrane concentrates in the mitochondria and draws electrons from entering the electron transport train.[4] Due to this, there is an increase in anaerobic metabolism, creating lactic acid and contributing to metabolic acidosis.[4] Free iron may lead to a decrease in coagulation not only through its damage to the liver but also through a possible impact on serine proteases.[4] In addition, free radicals are formed through reduction-oxidation reaction of free iron.[4] Free radicals are responsible for peroxidation of lipids and proteins, which then leads to damage of the effected organs.[4] Histamine and serotonin are released as a result of free iron.[4] The release of these neurotransmitters negatively affects the vascular system resulting in a decreased blood volume and, therefore, reduced cardiac output.[4]

Presentation of iron toxicity occurs in four stages. The first stage takes place from 30 minutes to 12 hours after ingestion.[5] Symptoms include vomiting, bloody diarrhea, abdominal pain, fever, and fatigue as a result of damage to the gastrointestinal tract.[5] Symptoms as a result of damage to other organs such as the central nervous system, cardiovascular system, pancreas, and liver may also present in this phase after more severe toxicity.[5] Usually no symptoms present during stage two (8-36 hours after ingestion) as a result of iron redistribution from the serum into intracellular compartments.[5] This time may be mistaken for resolution of symptoms after mild toxicity and patients should continue to be monitored.[5] During stage three liver injury/failure takes place.[5] Patients may

experience hypoglycemia, metabolic acidosis, cardiovascular collapse, shock, bleeding, coma, or seizures.[5] It is important to note that serum iron may not appear to be in a toxic range as free iron in the serum has been redistributed into intracellular compartments. Stage three lasts from 12-48 hours after ingestion of iron products.[5] During the final stage, 2-8 weeks after ingestion, a bowel obstruction, vomiting, or CNS effects may occur due to intestinal, pyloric, and antral stenosis.[5] Monitoring should include serum iron, total iron binding capacity, complete blood count, basic metabolic panel, and abdominal X-Ray within 6 hours of ingestion.[5]

Common iron containing medications (elemental iron) include ferrous gluconate (38mg), ferrous sulfate (65mg), ferrous fumarate (106mg), prenatal vitamins (~65mg), and multivitamins (~15mg).[6] When elemental iron concentrations surpass 60mg/kg in pediatric patients, serious adverse events and death may be experienced.[6] With this in mind, if more than 40mg/kg of elemental iron is ingested the pediatric patient should be taken to the emergency room for evaluation.[6] Treatment for iron toxicity includes several different options. If the abdominal x-ray shows non-dissolved tablets in the system then either whole bowel irrigation, gastric lavage, or endoscopic removal can be initiated.[7] These options will remove the iron containing products from the body, decreasing the amount of iron that can be absorbed into the body. Whole bowel irrigation is preferred when large quantities of iron-containing pills have been ingested.[7] If iron has made its way into the blood stream already, treatment depends on the free iron serum level. It is important to note that time since ingestion plays a role in interpretation of serum iron levels. When serum iron levels are under 55 μmol/L, no treatment is needed.[7] Serum iron levels between 55-90 μmol/L require observation.[7] With iron levels in this range it may be unknown whether iron is leaving the body or being redistributed into intracellular space. If no symptoms present then no treatment is needed.[7] Levels greater than 90 μmol/L require treatment with intravenous deferoxamine.[7] This agent will chelate with free iron in the serum, and this complex will then be excreted in the urine. Treatment with deferoxamine should be continued until symptoms resolve and urine is no longer discolored (pink/brown). [7] Children who are experiencing recurrent vomiting 2-6 weeks after ingestion should be evaluated for gastric outlet obstruction.[8]

Deferoxamine (Desferal) is an iron-chelating agent that is indicated for use in both acute iron intoxication and chronic iron overload.[9] This agent works by binding iron and forming a complex, which prevents the iron from participating in chemical reactions.[9] This agent does not affect iron that is bound by transferrin, cytochromes, or hemoglobin.[9] In addition, this medication does not affect the excretion of other electrolytes or trace metals.[9] Metabolism of deferoxamine is not yet understood; however, the formed complex is excreted primarily through the kidneys, which gives urine a characteristic red color.[9] Due to its renal excretion, deferoxamine is contraindicated in patients with renal impairment or anuria.[9] In patients who receive deferoxamine in high doses, for long periods of time, or if this agent is

administered in patients with low ferritin levels, reversal ocular and/or auditory disturbances may be observed.[9] These may include: blurry vision, cataracts, decreased visual acuity, visual defects, scotoma, corneal opacities, retinal pigmentary abnormalities, tinnitus, and hearing loss.[9] Other adverse events that have been observed include increases in serum creatinine, acute renal failure, and renal tubular disorders.[9] In patients with low ferritin levels, high doses of deferoxamine may cause growth retardation, which may increase after a dose reduction.[9] Administration of high intravenous doses of deferoxamine may also cause respiratory distress syndrome. This agent should be administered intramuscularly (IM) or by slow intravenous (IV) or subcutaneous infusion to prevent flushing of the skin, urticaria, hypotension, and shock.[9] Intramuscular administration is preferred for all patients who are not in shock.[9] Safety and effectiveness of this product have not been established in patients less than three years old.[9] The dose of deferoxamine in the situation of acute iron intoxication is 1000mg IM followed by 500mg every 4 hours.[9] 500mg doses may be repeated every 4-12 hours as needed based on clinical response, with a maximum dose of 6000mg in 24 hours.[9] This medication should only be administered via an intravenous route when the patient is experiencing cardiac collapse. If the patient's condition improves then intramuscular administration should take the place of intravenous infusion.[9] Deferoxamine 1000mg (IV) should be administered at a rate not greater than 15mg/kg/hour followed by two doses of 500mg over 4 hours if needed.[9] Subsequent doses of 500mg may be given over 4-12 hours if required, with a total daily allowance of 6000mg within 24 hours.[9] There is currently no antidote for deferoxamine, but this agent is readily dialyzable.[9]

Adult patients with children at home should be made aware that this medication should be kept in a safe location, out of reach of the children. The safety cap should remain on any bottle of iron-containing products to impede children from opening and accessing its contents. Patients should be warned that if a child were to take this medication serious adverse events could occur, including death. If this is to happen, patients should give their child milk to drink immediately, which will decrease the acidity of the stomach and slow iron absorption. [10] It is suggested to gather the following information if possible; patient's age, weight, current condition, the name of the ingested product, the time the product was ingested, and the amount that was ingested.[11] Parents should seek medical attention immediately if the amount ingested is unknown or if the time from ingestion is unknown. Parents may be directed to triage.webpoisoncontrol.org and/or may be directed to call the poison control at 1-800-222-1222 or 911.[12]

Iron overdose in children is a prevalent issue throughout the nation, with many of these cases being preventable. Increasing knowledge in the community as to the serious implications after ingestion of iron containing products may aid in decreasing overdose cases. Major damage in an overdose situation can be seen mainly in the GI tract, liver, and heart. There are four phases that occur after ingestion of iron

that leads to adverse effects of toxicity. The final phase may take place up to 8 weeks after ingestion has occurred. It is also important to note, the second phase is accompanied by no symptoms, which may be mistaken for a resolution of toxicity when an unknown amount of iron was ingested. Careful monitoring of the child should occur to ensure the child's safety until it is known that serum iron is below a toxic level. Treatment options may include: whole bowel irrigation, gastric lavage, endoscopic removal, or chelation with deferoxamine. Medical attention should be sought immediately after it becomes known that an overdose has occurred. Parents and guardians of children should be made aware to contact poison control, 911, or bring their child to the nearest hospital.

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Annual Review of Changes in Healthcare

Agricultural Antibiotics and Their Impact on Human Health

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One of the more revolutionary discoveries in modern medicine within the last century was the serendipitous discovery of penicillin by Alexander Fleming in 1928. Since then, several more antibiotic drug classes have been discovered and synthesized by researchers to specifically target different pathogens by their unique characteristics; +/- gram stain, aerobic, non-aerobic, etc. Unfortunately, the selection of inappropriate antibiotics and poor antibiotic stewardship have led to an increase in antibiotic resistant pathogens. The US Center for Disease Control and Prevention (CDC) report estimates approximately 2 million illnesses and 23,000 deaths annually are directly attributable to antibiotic resistant pathogens.[1] The CDC has cited antibiotic resistant pathogens as a top threat to global health and has testified before US Congress in 2010 with the FDA and USDA that there is a definite association between the use of antibiotics in food animal production and the antibiotic-resistance crisis in humans.[2]

An article by Aitken et al, has reviewed available evidence regarding the use of antibiotics in agriculture and their impact on human health.[3] In the United States, approximately 80% of all antibiotics consumed are for agricultural purposes and sold over the counter without any veterinary oversight.[3] Antibiotics have been used in agricultural livestock since the 1950's when it was discovered that their addition into feed significantly accelerated animal growth rates.[3] Additionally, antibiotic use in livestock has been used for purposes of feed efficiency and disease prevention.[3] The increased use of antibiotics in agriculture has led to the selection of resistant bacterial species among the livestock; analogous to their inappropriate and overuse in humans. The prevalence of resistant bacteria in agricultural livestock holds important safety implications for public health as transmission mechanisms of resistant bacteria from agriculture livestock to humans have been well documented and studied.[4-7]

The most straightforward transmission mechanism is direct transmission from farm animals to farmers and other animal handlers.[4] Epidemiological studies have found resistant antibacterial patterns in farms and farmworkers but not spread out to the community at large.[4] Environmental contamination has been studied to be another mode of transmission. Environmental sampling from large industrial farms has discovered a prevalence

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Volume 1, Issue 1

of resistant pathogens in waste laden soil and ambient air surrounding the farm and community at large.[5] Additionally, spillover from contaminated wastewater has been attributed to resistant pathogen containing soil samples in studies.[6] Lastly, some evidence has been documented of transmission by the consumption of undercooked animal products that contain resistant pathogens.[7] There may be other transmission mechanisms that have not yet been elucidated or discovered, but nonetheless the available evidence of transmission to humans should be of concern to public health.

With the availability of data supporting the impact of antibiotics in agriculture on human health, regulations aimed at decreasing the amount of antibiotics used in agriculture have begun to be developed and implemented.[3] It should be noted that antibiotic use in agriculture is only one piece of the puzzle; antibacterial stewardship efforts for increasing appropriate use in humans should continue to be sought. It is important for health care providers and policy makers to understand these associations to inform discussion, policies and other actions aimed at combating the antibiotic resistance epidemic.

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