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THE PHARMACY AND WELLNESS REVIEW

Editorial

The Haunting of Medical Literature

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Abstract

Ghostwriting, or using the names of academic researchers to validate studies commissioned by pharmaceutical companies, has become a growing concern within medical literature. Omission from authorship of the names of individuals making considerable contributions to a paper is one of the most significant aspects of ghostwriting. Policy prohibiting medical ghostwriting is lacking, and it is nearly impossible to prevent the practice without strict and thorough guidelines. More strict guidelines banning ghostwriting, denying government funds to organizations without such policies, and development of databases to track offending authors and organizations could decrease the impact of ghostwriting in medical literature.

Background

Clinical evidence has come to be revered as the standard of truth in medical practice. Pharmacists turn to clinical literature to make sound recommendations for patient drug therapy. It is often assumed that the integrity and validity of a published paper is ensured by referring to literature in esteemed, peer-reviewed journals. However, ethical considerations and conflicts of interest in authorship are slipping through quality assurance systems employed by these journals and threatening the foundation of medicine. *Ghostwriting*, or using the names of academic researchers to validate studies commissioned by pharmaceutical companies, has become a growing concern within medical literature.[1] Also concerning may be the use of *publication planning*, a form of systematically populating medical literature on the corporate scale. Publication planning is conducted by a team of people employed by a pharmaceutical manufacturer in an attempt to control every possible aspect of public information available about a drug of interest.[2] Publication plans include strategies for conducting explicit trials that yield desired results combined with the carefully timed release of information to specific target audiences. In some cases, the planning team may be more responsible for manuscripts submitted to medical journals than the respected author(s) appearing on the page.

Contributing Factors

The first factor contributing to medical ghostwriting is the definition of authorship. The correct protocol for listing authors is complicated by historical methods of listing authors alphabetically or listing the head of department as lead author as a sign of respect.[3] Currently, the International Committee of Medical Journal Editors defines authorship as fulfilling all of the following criteria for authorship: substantial contribution to conception and design, acquisition of data, or analysis and interpretation of data, drafting the article and/or revising it critically for important intellectual content, and final approval of the version to be published.[4] Omission of the names of individuals making considerable contributions to a paper from authorship is one of the most significant aspects of ghostwriting. More importantly, with the title of author comes a responsibility to ensure that the paper's content, intent and findings are based on the results of the study and scientific principle and not skewed by financial or political gain.[5] Authors list disclosure statements to inform the reader of existing conflicts of interest; however, the term "conflict of interest" is difficult to define. These conflicts typically include employment, grants and other financial support, but the lines become blurred when referring to patent rights, personal relationships or political ties. When the true authors are excluded from publications, they cannot be held responsible for the integrity of their work.

Policy prohibiting medical ghostwriting is lacking. In an evaluation of 50 of the top academic medical centers in the United States, 52 percent had no published policy regarding authorship or ghostwriting.[1] Without a policy in place, it is nearly impossible to stop this type of unethical misconduct. While the responsibility of honesty and disclosure lies with the author, there are few tools available for editors to police authorship validity.[5] A mere 8.8 percent of journals have a policy for verifying author claims and conflicts of interest.[6]

A Case of Ghostwriting

An example of ghostwriting that is thought to significantly impact the medical literature was when a pharmaceutical manufacturer attempted to prove that their drug could be used as an antidepressant in adolescents.[7] This study's results were published in the *Journal of the American Academy of Child and Adolescent Psychiatry* and listed 22 authors. The idea for the study came from the primary author and was accepted and conducted by the pharmaceutical manufacturer. However, the result of this study and similar studies showed no efficacy for the drug in adolescents compared to placebo. The manufacturer worried that the lack of efficacy in pediatrics would possibly make the medical community question the efficacy of the drug in general. Therefore, the manufacturer decided only to publish the positive findings from the study. A medical publishing company was hired to draft the positive information and prepare it for publication.

A synopsis of the clinical report was provided to the ghostwriter in the medical publishing group who used this shortened report to write the first draft of the manuscript. The ghostwriter also was found to have contributed to the article by developing and implementing a publication plan, responding to peer-reviews, and providing the primary author with drafts and cover letters.

Research looking into the communication between the listed authors and employees at the medical publishing company showed that many of the 22 listed authors had little to no involvement with the article. The ghostwriter was actually the primary writer of the article drafts, even though not listed as such. Also, it was shown that the second and third authors made only minor edits to the article throughout the process. Many of the authors were shown to have only made small edits to one of the drafts, having only assisted in running the study, or having made no recognizable contribution at all.[7]

A major issue with the first draft was that there were noticeable differences between it and the final clinical report, even though this was the source used to write the first draft. In the clinical report it is stated that only two primary outcomes were measured. In the first draft, eight primary outcomes were mentioned; four of these outcomes showed increased efficacy of the drug over placebo, which contradicts the findings of the study. Also, the line between the primary and secondary outcomes was blurred. After peer review, the article was edited again to include only the original two primary outcomes, but the information was presented in such a way that one of the outcomes appeared to be positive and reinforced the idea of efficacy for the drug. The side effects of the medication were inconsistent with the original report as well, and the seriousness of some listed side effects was not expressed.[7]

The results of this study being published include many clinicians believing the drug to be an effective and highly tolerable medication for adolescents. In 207 articles published since 2008, this study was mentioned and used as evidence that the drug is effective for use in adolescents. Only 31 of these articles correctly presented the information from the original study and showed slight skepticism over the results of the publication.[7]

Possible Solutions

Strict definitions of authorship need to be included in the policies of both medical journals and academic medical centers. It is not enough to condemn ghostwriting; the term needs to be extensively defined to be enforceable.[1] This strategy can further be amplified by government funding denying grants to institutions that lack these stringent ethical policies. Enforcement of these policies could be further reinforced by journals requiring listed article authors to sign a statement guaranteeing the integrity of their article and holding them accountable if dishonesty is suspected.[8] If violation of these policies is proven, offenders could be punished by revoking government funding, refusing to publish subsequent works by the author, and enforcing legal responsibility for falsifying documents.[1] These exclusions could be made possible by compiling an online database for easy access to a list of an author or institution's ethical infractions.[8]

Discussion

Ghostwriting will not be stopped until all levels of medical publishing commit to higher standards for literary ethics. Practitioners have a right to be informed of these conflicts of interest in literature so they can make their own decisions about the clinical validity of the evidence they are reading. Ghostwriting and publication planning allow publication of biased or incomplete information that may be harmful to patients who begin therapy with a medication with side effects and risks that are not fully disclosed. Many patients now may be suffering from severe adverse effects of medications because the dangers were not known and the treatment was marketed as being safe and effective. Ghostwriting is an emerging problem in medical writing that not only has ethical implications, but also affects patients and their wellbeing. The quality of medical care provided to patients is only as strong as the integrity of the literature that backs it.

Citations

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Recent Advances Spark Significant Guideline Change: Antiretroviral Therapy (ART) at High CD4+ Counts in the Treatment Naïve Patient

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Objectives:

After completion of this program, the reader should be able to:

1. Identify the pertinent laboratory values and/or symptomatology required for antiretroviral therapy initiation in treatment-naïve HIV patients.
2. Describe the limitations of early versus deferred treatment for HIV infection.
3. List the factors that limit patient adherence to antiretroviral therapy.
4. Identify the significant changes made to the newest version of the NIH HIV treatment guidelines.

Abstract

Human immunodeficiency virus (HIV) targets CD4+ lymphocytes, a critical component to proper functioning of the human immune system. HIV is a significant public health concern, having resulted in over 27 million deaths since its discovery. Currently, several different treatment options exist, with combination antiretroviral therapy (ART) at the forefront. Despite the success of ART therapy, there are number of problems, including poor patient compliance. Due to this, the appropriate time to initiate therapy in the treatment naïve patient is under continuous scrutiny. Recently, several trials have demonstrated evidence suggesting that initiating ART at high CD4+ counts in the treatment naïve patient is beneficial in preventing outcomes such as progression to AIDS and death due to complications from HIV. This review will discuss two trials influential in the recent change in The National Institute of Health's guidelines on therapy for treatment naïve patients. The trials reviewed here are the North American AIDS Cohort Collaboration on Research Design (NA-ACCORD) and the Antiretroviral Therapy Cohort Collaboration (ART-CC). Despite the success of therapy, it is associated with many negative side effects and high cost, which may affect patient compliance, lead to possible drug resistance and result in treatment failure. Along with the new evidence presented in clinical trials, these factors also must be considered when initiating therapy in the treatment naïve HIV patient.

Background

Human immunodeficiency virus (HIV) infects cells of the immune system and progressively leads to the destruction or deterioration of immune function.[1] HIV normally infects humans by targeting a type of white blood cell known as CD4+ T lymphocytes, which are involved in cell-mediated immunity. Viral particles bind to specific receptors on the cell surface and fuse with the cell. The virus can then enter the host cell and insert its viral DNA into the normal DNA of the host, forcing the newly infected cell to produce additional copies of HIV. These new copies of HIV can go on to infect other cells, leading to a progressive decline in the number and function of CD4+ T lymphocytes and attenuation of the immune system. After causing a significant decline in immune function, HIV can progress into a more serious form known as acquired immune deficiency syndrome (AIDS). AIDS is clinically defined as a CD4+ count of less than 200 cells/mm^3 or a documented AIDS-defining illness. HIV represents one of the world's greatest public health challenges, as it has claimed more than 27 million lives since its discovery. The HIV/AIDS epidemic continues to take nearly 2 million lives each year.[2] More than 33 million people worldwide, including almost 1 million in the United States alone, currently live with HIV/AIDS. HIV can be transmitted via a number of different mechanisms including unprotected sexual intercourse, contaminated blood transfusions, or the sharing of contaminated needles. Infected mothers also can transfer the virus to a child during pregnancy, birth or breastfeeding. Certain patient populations, including men who have sex with men (MSM), African Americans, and Hispanic/Latino Americans are at a disproportionately increased risk for contracting the virus.

As a result of increased patient education on prevention and protection, the spread of HIV has decreased in recent years.[3] However, the total number of infected individuals continues to rise as they are identified earlier and treated with more advanced medication regimens. Antiretroviral therapy (ART) blocks HIV's activity on CD4+ cells by targeting different stages in the HIV lifecycle and decreasing the overall viral load in infected individuals. HIV antiviral therapy includes a combination of the following drug classes: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), entry inhibitors, and integrase strand transfer inhibitors (INSTIs). ART involves various combinations of the antiviral drug classes. There are three preferred regimens for treatment naïve patients in the current NIH guidelines.[4] The regimens include a 2-NRTI backbone along with either an NNRTI, PI (ritonavir boosted) or INSTI. While the efficacy of antiretroviral therapy in slowing the progression of HIV and maintaining higher CD4+ counts has long been established, there is disagreement about when such therapy should be initiated. Over the past decade, several large-scale clinical trials have studied the risks and benefits of initiating ART at higher CD4+ counts, resulting in changes to the NIH guidelines for antiretroviral therapy in treatment naïve HIV patients.

NA-ACCORD

The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) evaluated the rate of death for treatment naïve patients who initiated ART therapy within different thresholds of CD4+ counts.[5] Patients in two different CD4+ count ranges, either 351-500 cells/mm^3 or greater than 500 cells/mm^3, were allowed to initiate or defer ART therapy as a part of their HIV treatment when entering the trial. Patients who initiated ART therapy more than six months after the start of the trial were included in the deferred group. A total of 8,362 patients, were included in the first analysis, [who contributed 23,977 person-years of follow-up], which looked at patients whose baseline CD4+ counts were between 351-500 cells/mm^3. ART therapy was initiated in 25 percent of patients within six months, while the remaining 75 percent deferred therapy. The second analysis included 9,155 patients (who contributed 26,439 person-years of follow-up) whose CD4+ count was greater than 500 cells/mm^3 at the beginning of the trial. In this group, 24 percent of patients initiated therapy early, and 76 percent deferred for greater than six months. The results of this study were significant because they assessed HIV patients with CD4+ counts above the guideline recommendation at that time, which did not recommend initiation of ART until CD4+ count decreased to less than 350 cells/mm^3. Throughout the study, the CD4+ counts and rate of death for patients in each group were assessed. A statistically significant increase in the risk of death for patients who deferred therapy was seen in both patient groups. The relative risk of death was 69 percent higher ($P<0.001$) for patients who deferred therapy with a CD4+ count of 351-500 cells/mm^3 and 94 percent higher in patients who deferred when their CD4+ count was greater than 500 cells/mm^3. The large patient population and significant duration of observation gave this trial strong external validity and allowed death to be used as an endpoint rather than an HIV/AIDS related biomarker. The deferment group in each CD4+ count range essentially served as a control for the study and allowed for an effective analysis of when to initiate ART therapy for patients based on their CD4+ count. No randomization or blinding of study participants was done in this study. However, the use of death as an endpoint limited the risk of bias in the results. Relative risk adjustments for confounding variable such as intravenous drug use and hepatitis C infection were performed, although a sensitivity analysis suggested that due to the size of the trial, confounding would have had to have been unnaturally large to affect the results. These adjusted relative-risk calculations also demonstrated an increased risk of mortality for the deferment group in each of the respective cohorts.

ART-CC

The Antiretroviral Therapy Cohort Collaboration (ART-CC) was an analysis of 12 cohort studies performed in Europe and North America between 1995 and 2003.[6] The study evaluated ART-naïve HIV patients and the progression of their disease once ART was initiated. The trial evaluated five prognostic variables indicative of disease progression, including CD4+ cell count, HIV-1-RNA level, injection drug use (IDU), age, and clinical AIDS. A total of 22,217 patients were included in the cohort database. From the initiation of ART, 20,379 of the patients were analyzed. Due to a lack of CD4+ cell counts between months three and nine during the trial, only 16,167 were included in the analysis from six months after initiation. For each of the variables, a hazard ratio was calculated for patients who progressed to AIDS before death and patients who died prior to the progression to AIDS. After five years, the risk for both endpoints, progression to AIDS followed by death or death alone, ranged from 5.6-77 percent. For example, patients who were less than 30 years old, were infected with HIV via some means other than IDU, had a CD4+ count of less than 350 cells/mm^3 at therapy initiation and had an HIV-RNA level below 5 log copies/ml possessed only a 5.6 percent risk of death over a five-year period. Patients who were 50 years old or older, became infected with HIV via IDU, started ART with clinical AIDS and a CD4+ count of less than 25 cells/mm^3, had an HIV-1-RNA level equal to or greater than 5log copies/ml and whose disease had progressed to AIDS had a 77 percent risk of death over the course of the trial. The results of this study demonstrated the significance of CD4+ cell counts as an indicator of overall survival in HIV patients. The hazard ratios (95 percent CI) ranged from 0.18 for patients with a six-month CD4+ count of greater than 350 cells/mm3 to 0.75 for those with a six-month CD4+ count ranging from 25-49 cells/mm^3. This study demonstrated strong internal validity due to its large size and adjustment in the hazard ratios for confounding variables. A limitation of the study was the lack of cause-specific mortality data for patients in each of the respective cohorts.

Updated Guidelines

Studies such as the NA-ACCORD analysis and ART-CC trial have contributed to the increasing evidence in support of early ART therapy initiation in HIV patients. As a result of these and other similar trials, a panel from the Department of Health and Human Services made significant changes to the current ART therapy guidelines with the goal of providing health care professionals with recommendations for HIV treatment that reflected the findings of the most recent clinical trials. A full version of the new 2010 NIH guidelines can be viewed online at www.aidsinfo.nih.gov.[4] Among the many modifications to the guidelines, the panel made several suggested changes to the timing of ART therapy initiation in treatment naïve patient. Citing evidence of decreased mortality in the NA-ACCORD and ART-CC clinical trials, the panel now recommends initiating therapy in all patients with CD4+ counts 500 cells/mm^3 or less. While the benefits of initiating therapy earlier were clearly demonstrated in the above clinical trials, the panel remained concerned about the long-term impact of side effects on patient adherence and the overall success of treatment. As a result of the NA-ACCORD trial, the panel also made a recommendation for patients with CD4+ counts of greater than 500 cells/mm^3. However, given the lack of supporting evidence from other cohorts or randomized clinical trials, the panel chose to classify initiation of ART therapy in these patients as optional and something to be considered on a case-by-case basis. In all recommendations made by the panel, they stressed the importance of assessing each individual patient's commitment to lifelong ART therapy and adequately explaining the associated benefits and risks before initiating therapy.

Cost

Patients who choose to begin antiretroviral therapy as a part of their HIV treatment are making a lifelong commitment to expensive medications. One argument against initiating such high-priced medications earlier in the course of HIV progression is that the costs of treatment will be unnecessarily increased. A 2001 study on the cost effectiveness of antiretroviral treatment found that patients who initiated combination therapy at 500 cells/mm^3 could expect to live an average of 9.1 years after starting treatment and would incur a lifetime medical cost of $104,100.[7] Patients in the study who chose to defer treatment until their CD4+ counts fell below 200 cells/mm^3 were expected to live an additional 8.51 years at a total treatment cost of $98,000. The results also showed an increase in the number of opportunistic infections experienced by HIV patients who deferred antiretroviral therapy. Over the course of many years of treatment, the costs associated with initiating therapy early are relatively

small compared to the demonstrated increase in life expectancy and decrease in the risk for opportunistic infections.

Patient Adherence and Adverse Events

Patient adherence to ART therapy was not addressed in either study cited by the updated treatment guidelines, but remains a concern for practitioners and patients because it directly correlates with treatment success. Specifically, the most common cause of antiretroviral treatment failure in HIV patients is non-adherence. Pill burden, timing, tolerability, cost and interactions all limit patient adherence. Zidovudine (AZT) was the first antiretroviral medication brought to the market in the 1980s. Patients were required to take AZT five times daily and experienced a number of debilitating side effects. Although newer, more tolerable antiretroviral drug therapies continue to become available, each current class of antiviral medications has general side effects that can affect patient adherence. NRTIs can cause mitochondrial toxicity including lactic acidosis, hepatic steatosis and pancreatitis.[4] NNRTIs can produce rashes and hepatic dysfunction.[4,7] PIs cause gastrointestinal disturbance (nausea, vomiting, diarrhea), bleeding problems, hepatotoxicity and metabolic issues including hyperlipidemia, fat maldistribution and insulin resistance.[4,8] Enfuvirtide, currently the only FI on the market, is administered subcutaneously and can cause injection-site reactions, bacterial pneumonia, insomnia, nausea and diarrhea.[4,9] Hepatotoxicity, fever, rash and upper respiratory tract infection are common side effects seen in maraviroc, an entry inhibitor.[4,10] Raltegravir is an INSTI, the newest class of HIV antiretroviral drugs, and has been associated with an increase in total cholesterol.[11] In addition to tolerability, pill burden also affects patient adherence. The availability of combination antiretroviral drugs has helped curb some of these adherence issues. In addition, drug-drug and drug-food interactions exist and are considered in therapy and monitoring. Pharmacists play an important role in screening for drug interactions, educating patients on side effects and the importance of adherence, as well as screening for other health issues and administering appropriate immunizations. Overall, patient adherence must be managed by all clinicians, including pharmacists, in order to prevent progression of the disease and improve quality of life.

Drug Resistance

Antiretroviral drug resistance is an important consideration in the treatment of HIV patients because it can have a significant impact on the success of ART therapy and lead to increased mortality.[13,14] Opponents of early antiretroviral initiation claim that using these drugs early in the course of HIV progression can increase the risk for resistance and limit future treatment options for patients.[15] Resistance to antiretroviral drugs is caused by mutations in the viral particles that result in different forms of HIV within an individual. Some of these variants of HIV are more resistant to antiretroviral drugs and can lead to a decrease in the effectiveness of treatment. One of the most influential factors in developing resistance to antiretroviral drugs is poor adherence to medication regimens. Patients who choose to initiate therapy and are subsequently poorly adherent expose themselves to antiretroviral drugs but do not fully suppress the replication of the virus. The virus then can continue to replicate in the presence of subtherapeutic drug concentrations, and the risk for mutant strains of the virus developing is increased. The risk of developing resistance to three major classes of antiretroviral drugs, NRTIs, NNRTIs and PIs, has been shown to decrease if treatment is initiated at higher CD4+ counts.[16,17] In order to reduce the risk of drug resistance and maximize the effectiveness of antiretroviral therapy, pharmacists and other clinicians must stress the importance of medication adherence to patients beginning treatment.

Conclusion

The benefits of initiating therapy at CD4+ counts above 350 cells/mm^3 were clearly demonstrated by the NA-ACCORD and ART-CC trials, and the newly refined guidelines reflect these new findings. However, treating HIV patients with ART therapy does have a number of limitations as well. Antiretroviral drug costs in the United States remain high, and regardless of the CD4+ count at which they are initiated, represent a significant financial burden for patients, insurance companies and government programs. Many classes of antiretroviral drugs also have serious potential side effects that can lead to increased morbidity and decreased patient adherence. A patient's adherence to their medication regimen is vital to slowing the progression of HIV and improving life expectancy. Most types of antiretroviral therapy include multiple different classes of drugs, and the resulting pill burden can lead to lower rates of adherence in patients, especially those with higher CD4+ counts that may not be experiencing an AIDS defining illness. Resistance to antiretroviral drugs, commonly the result of poor patient adherence, can limit treatment options for patients as they progress through the disease as well. However, despite these and other concerns, it is important to focus on the consistently improved patient outcomes demonstrated in early initiation groups from the reviewed clinical trials. Across almost all demographic groups, participants who initiated ART therapy earlier in the course of the disease were more likely to live longer and less likely to progress to clinical AIDS. The success of ART in HIV patients is dependent on a variety of different factors, and a careful assessment of the risks and benefits of treatment must be performed for patients considering initiating therapy at any point in the progression of the disease. Pharmacists and other health care professionals must play an active role in discussing the risks and benefits of treatment with patients and assessing the readiness to make a lifelong commitment to antiretroviral therapy. The most recent findings certainly do not signal the end of the debate on ART therapy, and HIV treatment will undoubtedly continue to be the focus of much discussion and research in the future.

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Assessment Questions

1. There are currently _____ people in the United States living with HIV/AIDS:
   a. 500,000
   b. 1 million
   c. 2 million
   d. 5 million

2. All of the following patient populations are at an increased risk of contracting HIV EXCEPT:
   a. Hispanic/Latino Americans
   b. Men who have sex with men (MSM)
   c. African Americans
   d. All of the above

3. Which of the following is NOT considered a preferred antiretroviral treatment regimen for treatment naïve patients:
   a. 2-NRTI + 1 PI (ritonavir boosted)
   b. 2-NRTI + 1 FI
   c. 2-NRTI + 1 NNRTI
   d. 2-NRTI + 1 INSTI

4. Which of the following CD4+ count values is the minimum at which an asymptomatic HIV-positive patient would not be classified as an AIDS patient:
   a. 500 cell/mm3
   b. 200 cells/mm3
   c. 100 cells/mm3
   d. 50 cells/ mm3

5. The 2010 NIH Guidelines state that antiretroviral therapy should be initiated in patients with each of the following CD4+ counts EXCEPT:
   a. 300 cells/mm3
   b. 350 cells/mm3
   c. 400 cells/mm3
   d. 600 cells/mm3

6. Results of a study conducted by Schackman et al published in 2001 suggested that patients initiating ART therapy at 500 cells/mm3 could expect to live an additional _____ years as a result of treatment:
   a. 9.1 years
   b. 7.5 years
   c. 6.3 years
   d. 10.6 years

7. All of the following are considered to be limitations to patient adherence with antiretroviral therapy EXCEPT:
   a. Pill burden
   b. Cost of treatment
   c. Requires inpatient administration
   d. Side effects

8. Protease Inhibitors are associated with which of the following side effects:
   a. Upper respiratory tract infection
   b. Insulin resistance
   c. Insomnia
   d. Renal failure

9. Which of the following is considered a role of the pharmacist in improving patient adherence and limiting adverse effects with antiretroviral drugs?
   a. Administering appropriate immunizations
   b. Screening for drug-drug and drug-food interactions
   c. Educating patients on common side effects of their medications
   d. All of the above

10. One argument against earlier initiation of ART therapy is that poor patient adherence will lead to an increased risk of:
   a. Side effects from current medications
   b. Clinically significant bleeding episodes
   c. Liver transplantation
   d. Resistance to antiretroviral drugs

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Program Content:	Strongly Disagree				Strongly Agree
The program objectives were clear.	1	2	3	4	5
The program met the stated goals & objectives;					
Identify the pertinent laboratory values and/or symptomatology required for antiretroviral therapy initiation in treatment-naïve HIV patients.	1	2	3	4	5
Describe the limitations of early versus deferred treatment for HIV infection.	1	2	3	4	5
List the factors that limit patient adherence to antiretroviral therapy.	1	2	3	4	5
Identify the significant changes made to the newest version of the NIH HIV treatment guidelines.	1	2	3	4	5
The program met your educational needs.	1	2	3	4	5
Content of the program was interesting.	1	2	3	4	5
Material presented was relevant to my practice.	1	2	3	4	5

Comments/Suggestions for future programs:

Thank You!

Answers to Assessment Questions - Please Circle Your Answer

1. A B C D **4. A B C D** **7. A B C D** **10. A B C D**

2. A B C D **5. A B C D** **8. A B C D**

3. A B C D **6. A B C D** **9. A B C D**

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Genetic Variations in a Cytochrome P450 Enzyme and the Effects on Clopidogrel Bioactivation and Metabolism

MaryAnne Ventura, fourth-year pharmacy student from Centre Hall, Pa.; Lauren Desko, fourth-year pharmacy student from Perrysburg, Ohio; Kimberly Gathers, fifth-year pharmacy student from Mercer, Pa.; Ashley Overy, fifth-year pharmacy student from Grafton, Ohio; David Kisor, B.S., PharmD, professor of pharmacokinetics, chair of the Department of Pharmaceutical and Biomedical Sciences

This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

ACPE Universal Activity Number (UAN): 0048-0000-11-001-H01-P

Objectives:

After completion of this program, the reader should be able to:

1. Describe the variables that account for differences in response to clopidogrel therapy and which accounts for the most variation in response.
2. List the clinical effects or complications that may result from a decreased patient response to clopidogrel.
3. Explain the various testing methods available to detect a variation that can result in decreased clopidogrel response.
4. Describe the various advantages and disadvantages of the currently available testing methods.
5. Discuss what constitutes a poor metabolizer and the risks associated with this phenotype.
6. Explain the pharmacist's role in advocating for and providing access to genetic testing.

Abstract

Clopidogrel, the top prescribed antiplatelet medication for individuals who have experienced a myocardial infarction or cerebral vascular accident or who have peripheral arterial disease, is administered orally as a prodrug. It relies on hepatic metabolism through cytochrome P450 enzymes for conversion to its active form. Current research shows that allelic variation in the gene coding for CYP2C19 is the main factor contributing to the variability of response associated with clopidogrel treatment. Through the promotion of genetic testing for variability in the CYP2C19 gene and competently interpreting test results, pharmacists have the opportunity to use these findings to significantly impact clopidogrel prescribing and dosing. By tailoring an individual's dosing regimen, pharmacists can maximize the efficacy of clopidogrel for a patient according to his or her genotype.

Introduction

Over the last 11 years, physicians have prescribed clopidogrel (Plavix®) to more than 100 million people.[1] Clopidogrel is commonly used to prevent thrombotic events in patients who have recently experienced a myocardial infarction (MI) or cerebral vascular accident (CVA) and in those who have established peripheral arterial disease (PAD). Given that clopidogrel is an orally administered prodrug, its efficacy is dependent on its bioactivation via hepatic metabolism. Cytochrome P450 enzymes, especially CYP2C19, are essential for the conversion to its active form.[2] Consequently, any variability in CYP2C19 can significantly impact the bioactivation of clopidogrel, thereby influencing its efficacy. As a result, the approved Plavix® product labeling cautions prescribers that reduced effectiveness is seen in patients with impaired CYP2C19 function.

Black Box Warning

In March 2010, the United States Food and Drug Administration (FDA) added a black box warning to the clopidogrel labeling to alert health care professionals that the drug may be less effective in a certain population of patients who are unable to convert it to the active form.[3] The black box warning states, "Clopidogrel hydrogen sulfate effectiveness is dependent on its activation to an active metabolite by CYP2C19. In patients who are CYP2C19 poor metabolizers, clopidogrel at recommended doses forms less of that metabolite and has a smaller effect on platelet function. Compared with normal metabolizers, poor CYP2C19 metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel at recommended doses exhibit higher cardiovascular event rates. Tests are available to identify a patient's CYP2C19 genotype; these tests can help determine therapeutic strategy. Consider alternative treatment or treatment strategies in CYP2C19 poor metabolizers." By encouraging the use of genetic tests, pharmacists can help in identifying patients who are poor metabolizers of clopidogrel, thus promoting the personalization and improved efficacy of clopidogrel therapy.

Normal Clopidogrel Metabolism

Platelet aggregation is a normal response to tissue injury; adenosine diphosphate (ADP) released from platelets activates neighboring platelets by binding to the $P2Y_{12}$ receptor, thus promoting platelet aggregation.[4] The active form of clopidogrel inhibits this platelet aggregation by irreversibly binding the $P2Y_{12}$ receptor and inhibiting the full activation of the glycoprotein IIb/IIIa adhesion receptors on platelets (Figure 1).

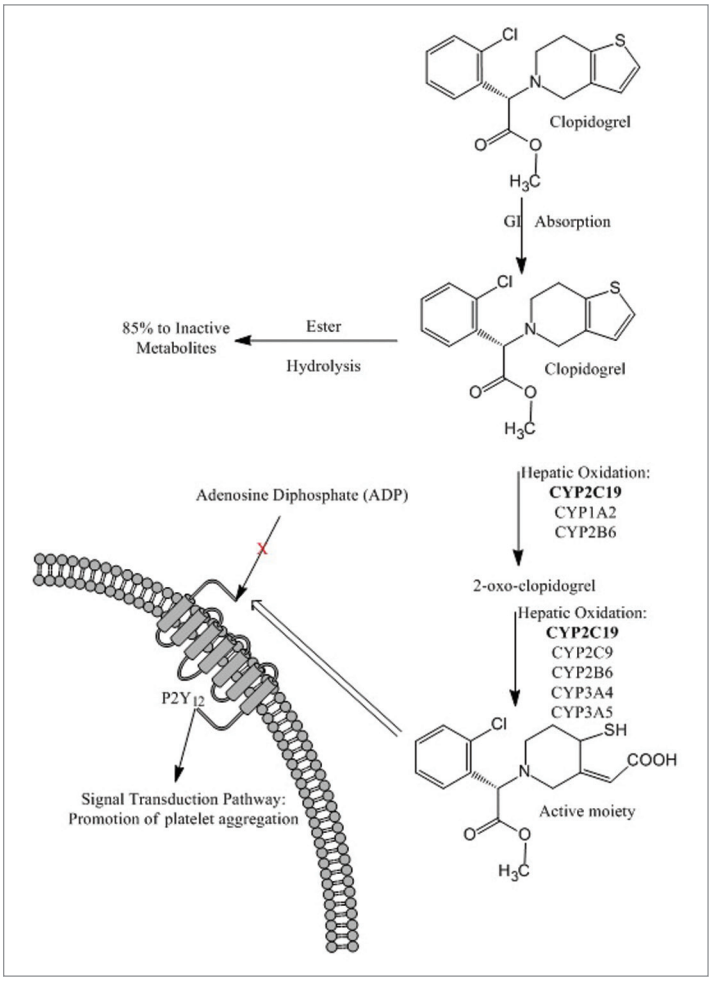

Figure 1. Bioactivation of clopidogrel via CYP450 system with CYP2C19 being the predominant activation pathway. Conversion of clopidogrel to the active moiety results in its mechanism of action as an inhibitor of adenosine diphosphate (ADP) induced platelet aggregation.

Following absorption from the small intestine, clopidogrel requires several in vivo activation steps for conversion to its active form (Figure 1).[4] Some of the absorbed drug is excreted back into the intestine via P-glycoprotein(P-gp)-mediated efflux pumps, thereby decreasing the amount of prodrug available for activation. Only about 15 percent of the orally administered dose of clopidogrel is metabolized by the CYP system in the liver to yield the active metabolite, while the remaining 85 percent is hydrolyzed to an inactive form by esterases in the blood (Figure 1).[5] The CYP2C19 enzyme in the liver has been identified as one of the most significant enzymes in regard to clopidogrel resistance. Several classifications exist pertaining to an individual's genotype for the CYP2C19 enzyme; to be considered a normal metabolizer, also referred to as an extensive metabolizer (EM), an individual must have no genetic disparities in the gene that codes for CYP2C19 and express the wild type allele (CYP2C19*1)[4,6,7,14] An intermediate metabolizer (IM) is a person with one "loss of function" allele, while a poor metabolizer (PM) has two "loss of function" alleles.[6] Intermediate and poor metabolizers will have a decreased activity of clopidogrel due to a decrease in the formation of the active compound.[14] There are five common mutations in the CYP2C19 gene, *2, *3, *4, *5 and *17.[4,14] The most common variants are the first four, while the CYP2C19*17 variant is associated with the ultra-rapid metabolizer phenotype.

Clopidogrel Resistance Due to Genetic Variants

Three main factors have been identified that contribute to the overall resistance of clopidogrel displayed in some patients; these include differences in gastrointestinal (GI) absorption, platelet receptor abnormalities, and variations in hepatic metabolism.[4] The GI absorption of clopidogrel is dependent on two main features: the activity of GI esterases and P-gp efflux pumps. Polymorphisms in the genes that code for P-gp efflux pumps have been associated with an increase in the GI efflux of clopidogrel.[9] Platelet receptor abnormalities, or polymorphisms in the genes coding for the glycoprotein IIb/IIIa or the $P2Y_{12}$ receptor, can cause decreased metabolite binding and subsequent decreases in platelet aggregation.

The factor with the greatest impact on the resistance to clopidogrel is the genetic variations in the CYP isoenzyme pathways of hepatic metabolism.[4] The polymorphism identified to have the most significant impact is that of the CYP2C19 gene. It is estimated that 33-50 percent of the population has a variant form of the CYP2C19 gene.[6] Full function of this gene, associated with the wildtype*1 allele, is required in both steps of clopidogrel metabolism: first for conversion of clopidogrel to 2-oxo-clopidogrel, and then for metabolism of 2-oxo-clopidogrel to the active compound (Figure 1).[2,10] Many studies have linked variations in CYP2C19 to an increased risk of death or non-fatal MI or CVA as well as a greater occurrence of in-stent thromboses. TRITON-TIMI 38 investigators (ClinicalTrials.gov Identifier No. NCT00097591) identified that carriers of the CYP2C19*2 allele had a significantly increased risk of death from CV events, non-fatal MI and CVA (p=.01) and were three times more likely to experience an in-stent thrombosis (p=.02).[11] The FAST-MI studies linked genetic variation in the gene coding for the given enzyme, especially the *2 allele, to significantly increase the risk of death, stroke, MI, revascularization and in-stent thrombosis; expression of any two of the variants associated with loss of function, particularly the *2, *3, *4, or *5 alleles, nearly doubled the risk of death or nonfatal MI or stroke within one year (p=.045).[9] The PRINC Trial demonstrated that if identified, individuals with genotypes indicative of poor response to clopidogrel, particularly those expressing the *2 or *4 alleles, could experience an increased degree of platelet inhibition if their dosing was modified from what is currently considered to be the standard dose.[12] The study showed that while wildtype carriers had better platelet inhibition two hours after a 600 mg loading dose compared to inhibition in *2 and *4 individuals (p=.026), individuals with the *2 and *4 alleles had greater inhibition than wildtype individuals with a 1,200 mg loading dose at four hours (p=.002). Additionally, *2 and *4 individuals responded better than wildtype individuals with a 150 mg maintenance dose compared to the standard 75 mg maintenance dose (p=.042).

By taking into account an individual's age, BMI, lipid levels and CYP2C19 genotype, approximately 22 percent of the variation of clopidogrel response can be explained.[13] This leads to the conclusion that assessment of the CYP2C19 genotype may prove to be a useful clinical tool for helping health care providers choose the most efficacious antiplatelet therapy and dosing regimen for a given patient.

Non-genetic Testing

Phenotyping can be performed to categorize the functional aspect of a particular drug metabolizing enzyme.[14] This is not a genetic test; rather, it involves the patient consuming a probe drug that utilizes the enzyme pathway of interest. Measurements are made using the probe drug and an inactive metabolite, and these measurements are then converted into a ratio that serves as the "metabolic ratio." This ratio is used to determine the metabolic rate that allows an individual to be characterized as an EM, PM or IM. These probe tests can be performed using a single probe, or a "cocktail" of several probe drugs can be utilized to assess multiple enzyme pathways concurrently. Before a "cocktail" is used, it must be determined that no drug interactions exist between any of the probes used to avoid confounding the resultant metabolic ratios.

The phenotypic categories can be used to quantify how a patient will metabolize a drug utilizing that certain enzyme.[14] The effect of being a PM depends on whether the drug in question is pharmacologically active or a prodrug. In the case of clopidogrel, a PM will experience a decrease in the bioavailability of the active form of the drug. Phenotyping may be difficult to perform clinically because the measurements are not taken until a number of hours after drug administration, therefore making this type of testing more suitable for a research setting.[14]

An additional testing option is the proprietary VerifyNow-P2Y12 test, a point-of-care assay that was developed by Accumetrics.[15] A small blood sample is taken, and an ADP agonist is used to stimulate platelet aggregation. The test then measures how well platelet aggregation is impaired by clopidogrel. Thrombin receptor agonists are also used to approximate the patient's baseline platelet aggregation.[5]

Genetic Testing

Molecular genetic testing entails examining the gene or genes that code for an enzyme to see which alleles are present. There are several genetic tests available to investigate how well an individual will metabolize clopidogrel. Two available tests are *AmpliChip*™, developed by Roche Diagnostics, and Quest Diagnostic's *AccuType*™ *CP*.[16-18] These two genetic tests involve taking a patient's blood sample and testing for variants in the CYP2C19 genes using polymerase chain reactions (PCRs), which is a method to make many copies of the genes so it can be more easily measured. A computer program then analyzes the PCR data and determines the genotype and corresponding phenotype of the patient.[16,17]

The *AmpliChip*™ test is designed to be able to have the results available in an eight-hour period.[18] However, the time it takes for a patient's blood to be drawn and tested and the results to be returned varies depending on the lab and test used. In order for these genetic tests to become more clinically useful in clopidogrel therapy, technology must be developed to make test results available prior to dosing. Research currently is being done on a technology that involves the use of a fluorescence-based assay that measures an energy exchange to distinguish the target DNA sequence that codes for the specific enzyme.[19] The goal is to develop a portable, low-cost and real-time assaying platform that could potentially be used for on-site genetic testing.

Advantages and Disadvantages of Genetic Testing

The costs of different genetic tests vary depending on the test and lab being used but generally range from $250 to $500.[20] These tests may be covered by a patient's insurance plan, though many insurance companies consider them to be "investigational, experimental or unproven."[6] Due to evidence that genetic variations in the CYP2C19 gene are associated with increased risks for the occurrence of adverse cardiovascular events and in-stent thromboses, using pharmacogenomics and genetic testing with clopidogrel therapy presents a real opportunity to decrease health care costs despite the added costs of the testing itself. The use of genetic tests can help the clinician identify and prevent situations in which patients undergo clopidogrel treatment that is rendered ineffective due to their genetic makeup. However, these tests also may identify the need for a treatment that is likely to be more effective but also more costly. The clinical application of this technology also has some drawbacks, including the invasive nature of these genetic tests, which require blood to be drawn. Moreover, including a genetic test before prescribing clopidogrel to a patient will increase turn-around time for a patient to receive the appropriate anti-platelet therapy.

Using genetic tests to determine if a patient has any polymorphisms in the gene for CYP2C19 may aid in individualizing and optimizing clopidogrel treatment.[12] In a study done at the Sinai Hospital in Baltimore, Md., those with the *CYP2C19*2* gene mutation demonstrated no difference in baseline platelet aggregation compared to those without the "loss of function" allele.[13] However, those with the mutation demonstrated greater residual platelet aggregation after clopidogrel therapy. After one year of follow-up, those with the *CYP2C19*2* genotype had higher rates of cardiovascular events compared to those without the mutation. This demonstrates the advantages of using genetic testing in conjunction with clopidogrel therapy.

Conclusion

Pharmacists can play a key role in increasing awareness and accessibility of genetic testing, especially in the area of clopidogrel prescribing and dosing. It is the responsibility of pharmacists to ensure that patients understand the benefits of these genetic tests. In conjunction with pharmacist-run anti-coagulation clinics, on-site genetic testing and subsequent clopidogrel dosing by a pharmacist could become a standard made available to patients. Pharmacists, in both community and hospital settings, may recommend to a prescriber an increased dose of clopidogrel or a change in therapy to an entirely different medication for patients who have been deemed PMs according to results of their genetic testing. Using data presented in the PRINC trial, pharmacists can advocate for patients who are classified as PMs of clopidogrel, based on their genotype concerning the CYP2C19 gene, to be treated with higher loading and maintenance doses. This will allow them to see platelet inhibition comparable to outcomes observed with the standard dosing in EMs. Such recommendations could consequently improve clinical outcomes for patients who would otherwise see no benefit from this pharmaceutical therapy; however, patients can only benefit from this type of intervention if their genotype can be quantified via genetic testing for variants in the CYP2C19 gene. The application of these genetic test results is an area of practice that pharmacists can embrace as part of the movement toward increased patient counseling and medication therapy management. The use of genetic testing in the prescription and dosing of

clopidogrel presents an opportunity for pharmacists in most practice settings to expand the degree of care provided to patients by encouraging the personalization of clopidogrel therapy. Rather than adhering to the current "one size fits all" method of prescribing, pharmacists have the opportunity to take a more proactive approach to customize antiplatelet therapy based on a patient's individual needs and significantly increase the efficacy of patient treatment with clopidogrel.

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Assessment Questions

1. Which of the following are utilized in genetic testing?
   a. *AmpliChip*™
   b. *AccuType*™
   c. VerifyNow-P2Y12
   d. A and B

2. AmpliChip™ uses _____ to determine genotype.
   a. Probe drug
   b. PCR
   c. ADP agonist
   d. None of the above

3. Which factor has been identified to contribute the most to variation in response to clopidogrel therapy?
   a. Variations in the CYP2C19 enzyme
   b. Platelet receptor abnormalities
   c. Activity of GI esterases
   d. Activity of P-gp efflux pumps

4. What is released from platelets during a normal response to tissue injury?
   a. PLC
   b. ATP
   c. ADP
   d. cAMP

5. What percentage of a normal orally administered dose of clopidogrel is metabolized in the liver to the active form?
   a. 85 percent
   b. 50 percent
   c. 25 percent
   d. 15 percent

6. An individual with two "loss of function" alleles is characterized as which type of metabolizer?
   a. Extensive metabolizer
   b. Intermediate metabolizer
   c. Poor metabolizer
   d. Normal metabolizer

7. According to the conclusions of the TRITON-TIMI study, all of the following are true for carriers of the CYP2C19*2 variant EXCEPT:
   a. Decreased risk of in-stent thrombosis
   b. Increased risk of death from cardiovascular events
   c. Increased risk of non-fatal MI or CVA
   d. Two of the above

8. Which are ways that pharmacists can be involved in genetic testing and clopidogrel dosing?
   a. Ensure that patients are aware of testing availability and benefits.
   b. Provide clinics or on-site genetic testing for patients.
   c. Recommend a change in dosage or therapy if indicated by test results.
   d. All of the above

9. According to the PRINC study, which options are available to optimize therapy for poor metabolizers of clopidogrel?
   a. Longer course of therapy
   b. Higher loading and maintenance doses
   c. Recommend switching to a different therapy
   d. B and C

10. All of the following are benefits of genetic testing EXCEPT:
   a. Prevention of futile therapy
   b. Rapid time frame to achieving appropriate clopidogrel therapy
   c. Decreased overall health care costs
   d. Decreased clinical complications

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Program Title: Genetic variations in a cytochrome P450 enzyme and the effects on clopidogrel bioactivation and metabolism
UAN: 0048-0000-11-001-H01-P **CEU's:** 0.1

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Pharmacy License #: **State:** **ONU Alumni? Y N**

Program Content:	Strongly Disagree				Strongly Agree
The program objectives were clear.	1	2	3	4	5
The program met the stated goals & objectives;					
Describe the variables that account for differences in response to clopidogrel therapy and which accounts for the most variation in response.	1	2	3	4	5
List the clinical effects or complications that can result in a decreased patient response to clopidogrel.	1	2	3	4	5
Explain the various testing methods available to detect a variation that can result in decreased clopidogrel response.	1	2	3	4	5
Describe the various advantages and disadvantages to the testing methods currently available.	1	2	3	4	5
Discuss what constitutes a poor metabolizer and what are the risks associated with this phenotype.	1	2	3	4	5
Explain the pharmacist's role in advocating for and providing access to genetic testing.	1	2	3	4	5
The program met your educational needs.	1	2	3	4	5
Content of the program was interesting.	1	2	3	4	5
Material presented was relevant to my practice.	1	2	3	4	5

Comments/Suggestions for future programs:

Thank You!

Answers to Assessment Questions - Please Circle Your Answer

1. A B C D	**4. A B C D**	**7. A B C D**	**10. A B C D**
2. A B C D	**5. A B C D**	**8. A B C D**	
3. A B C D	**6. A B C D**	**9. A B C D**	

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Any questions/comments regarding this continuing education program can be directed to Lynn Bedford, Advanced Administration Assistant for the Office of Continuing Education (e-mail: l-bedford@onu.edu, phone 419-772-1871).

Management of Hypertensive Emergencies in Pediatrics

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Abstract

As hypertension becomes more prevalent in the pediatric population, clinicians are more likely to encounter hypertensive emergencies in children, which require pharmacists and physicians to be educated on the therapeutic options for these emergencies. However, the strict governmental requirements on the testing of these drugs in pediatric patients have limited the amount of available evidence on which to base clinical decisions. This review will highlight the available evidence and preferred treatment options for the management of pediatric hypertensive emergencies.

Introduction

Historically only a disease of adults, hypertension is increasing in the pediatric population. Recent studies show that the prevalence of hypertension in school-age children is about 4-5 percent.[1] In children, hypertension is defined as systolic blood pressure and/or diastolic blood pressure greater than the 95th percentile for sex, age and height on at least three occasions.[2] In contrast to hypertension in adults, which is usually primary, hypertension in children is commonly due to secondary causes such as renal disease, cardiovascular disease, endocrine disorders and medications.[1]

Little data is available on the use of antihypertensive medications in children due to ethical concerns and strict testing requirements for the pediatric population.[1] With continued research and clinical experience, clinicians will have more evidence to guide decisions and select the most appropriate and efficacious medication. Practitioner familiarity with the pediatric population and available treatments for hypertensive emergencies will optimize patient outcomes. This review will present the possible medication options for the treatment of hypertensive emergencies in the pediatric population, with a focus on the dose, route of administration and other characteristics specific to each drug. Furthermore, roles for pharmacists in the prevention and treatment of these severe hypertensive episodes in pediatric patients will be discussed.

Severe Hypertension

Severe hypertension in children is defined as a blood pressure above the 99th percentile.[3] Hypertensive emergency can be identified by the presence of acute end-organ dysfunction. Clinical presentation of end-organ damage involve the central nervous system, eyes, heart, and kidneys and may manifest as seizures, retinopathy, cardiomegaly, congestive heart failure, tachypnea, and/or lethargy, among other presentations.[4] The type of acute end-organ damage determines the type of therapy used to treat these patients.

Pharmacotherapy for Hypertensive Emergencies

Hypertensive emergencies require immediate treatment. Several factors dictate which treatment option will be utilized, including the severity of the patient's clinical condition, type of end-organ damage, presumed cause, cardiac output, total peripheral resistance, and physician familiarity with the medications.[5] Hypertensive emergency is typically treated using intravenous (IV) medications to closely control reductions in blood pressure. The goal of treatment is to decrease blood pressure by up to 25 percent over the first six to eight hours, followed by a gradual reduction over the next 48 hours.[5,7] Treatment of hypertensive emergencies requires a controlled decrease in blood pressure to avoid severe hypotension, which may result in ischemia and necrosis due to changes in tissue autoregulation.[5]

Sodium nitroprusside

Sodium nitroprusside is an arteriolar and venous vasodilator with an instantaneous onset of action.[5] This advantage is somewhat offset by its 10-minute preparation time. The vial must be reconstituted with 5 percent dextrose in water or sterile water and then further diluted for continuous infusion via a volumetric infusion pump to allow for tightly controlled administration.[6] Additionally, the bottle, burette and syringe pump must be covered with an opaque protective covering to prevent degradation by light; amber plastic coverings are insufficient. Sodium nitroprusside decreases both cardiac preload and afterload with no chronotropic or inotropic effects.[7] It may be used when short-term reduction of cardiac preload and/or afterload is desired.[8] Cyanide toxicity is a concern with nitroprusside, and, according to manufacturer recommendations, failure to obtain the desired blood pressure control after maximum rate infusion (8-10 mcg/kg/min) for 10 minutes should result in termination of the infusion to avoid toxic cyanide levels.[6] Patients with hepatic or kidney dysfunction are more prone to accumulation of thiocyanate, and anuric patients should receive no more than 1 mcg/kg/min to avoid toxicity. Signs of cyanide toxicity may not appear until an hour after toxic levels have been reached. Administration of thiosulfate and methylene blue have been postulated as treatments for cyanide toxicity, but these should be used with caution as their routine use is not recommended. Nitroprusside may increase intracranial pressure and should not be used to treat compensatory hypertension due to aortic coarctation or arteriovenous shunting in patients with known inadequate cerebral circulation, or high-output heart failure.[6,7]

Nitroglycerin

Nitroglycerin is a potent vasodilator that reduces blood pressure by predominately decreasing preload and modestly reducing afterload.[9,10] It is mainly used as an adjunct in patients with hypertensive emergencies associated with acute coronary syndromes or acute pulmonary syndromes.[11] Its use is contraindicated in pericardial tamponade, restrictive cardiomyopathy and constrictive pericarditis.[6] The onset of action is

one to five minutes with a duration of action of five to 10 minutes after the infusion is discontinued.[9] Despite its favorable onset and duration, nitroglycerin is not considered a first-line treatment because of its potential to cause tachycardia and precipitous hypotension even in very small doses.[6,9] Methemoglobinemia has been observed in adults when doses greater than 7 mcg/kg/min were used; tachyphylaxis also has been seen in adults and can often be reversed by an eight-hour nitrate-free interval.[6] The infusion should be administered from a glass bottle using a non-polyvinyl chloride (PVC) set to prevent drug adsorption to the tubing. If a PVC set must be used, higher than expected doses may be required due to loss of drug in the tubing.[6]

Labetalol

Labetalol is a selective α_1 and non-selective β-blocker. It has an onset of action within two to five minutes and can be administered as an intermittent or continuous infusion.[5,9] Because labetalol is not cardioselective, it reduces blood pressure by producing both a modest reduction in heart rate and a decreased systemic resistance through vasodilation.[7] It may be a safe choice in patients with cerebrovascular disease or increased intracranial pressure because it does not further increase cerebral blood flow or intracranial pressure.[4] Labetalol is contraindicated in asthma, chronic lung disease, heart block, cardiogenic shock and heart failure. Dose adjustments are not required in patients with severe renal or hepatic dysfunction.[5] Like other β-blockers, labetalol may mask symptoms of hypoglycemia such as tachycardia.[7] If using labetalol in a patient suspected of pheochromocytoma or stimulant intoxication, specific assay methods such as high-performance liquid chromatography with solid-phase extraction should be used to avoid false-positive urine catecholamine tests. Additionally, labetalol may produce false positives if using the Toxi-Lab A or Emit-d.a.u. amphetamine assays.[6]

Esmolol

In contrast to the non-selective β-blocker labetalol, esmolol is a β_1 selective receptor antagonist that has an onset of action within seconds.[4,12] A significant advantage of esmolol is its short duration of action, approximately 10 to 20 minutes, and its extremely short half-life, which allows it to be easily titrated. Esmolol reduces blood pressure by decreasing cardiac output.[13] It is thus contraindicated in sinus bradycardia, in a greater than first-degree heart block unless a functional pacemaker is in place, cardiogenic shock and overt heart failure.[6] Esmolol is safer than labetalol in patients with asthma and obstructive lung disease but should still be avoided; if necessary, the smallest dose possible should be utilized.[7] Like labetalol, esmolol does not increase cerebral pressure or blood flow.[13] It does not require dose adjustments in renal or hepatic disease, although the half-life of the active metabolite may be increased tenfold in organ dysfunction.[6,7] Esmolol is more likely to cause thrombophlebitis and irritation when infused at concentrations greater than 10 mg/ml, and it may interfere with glucose and cholesterol tests.[6]

Hydralazine

Hydralazine is an arteriolar vasodilator with an onset of action of 30 minutes.[5] The duration is fairly unpredictable and may range from four to 12 hours.[7] Hydralazine is not as potent as sodium nitroprusside and may cause reflex tachycardia requiring administration of a β-blocker.[5] If a β-blocker and hydralazine are used simultaneously, the dose requirements of hydralazine are reduced.[6] This drug can produce renin-mediated sodium and fluid retention, which may necessitate the use of diuretics.[6,7] A unique feature of hydralazine is that it may be given intramuscularly to a patient who does not have an intravenous line established but requires immediate treatment.[7] It also can be given by IV push. Hydralazine should be used with caution in patients who have suffered a cerebrovascular accident.[6] It is contraindicated in patients with coronary artery disease and mitral valvular rheumatic heart disease. Especially in slow acetylators, hydralazine has the rare potential to induce systemic lupus erythematosus and related syndromes such as glomerulonephritis; if these develop, therapy with the agent should be re-evaluated. Hydralazine does require dose adjustments for patients in renal failure and further adjustments may be made if acetylator status is known. It should never be diluted in sugar-containing solutions due to the formation of toxic hydrazones. Peripheral neuritis may develop and may be treated with pyridoxine.

Nifedipine

Nifedipine is a calcium channel blocker administered sublingually and has an onset of action within 15-30 minutes.[5,11] This drug has the potential to produce a precipitous drop in blood pressure, which has made its use controversial. It is considered safer in children than it is in adults, and using a dose below 0.25 mg/kg may help minimize the risk of hypotension.[13,14]

Nicardipine

Nicardipine is also a calcium channel blocker.[5] It has a favorable onset of action within minutes.[4,9] Nicardipine is an excellent medication for emergencies because it can be easily prepared and titrated, although it can only be given by continuous IV infusion.[5,6] It has been shown to be safe and effective in treating hypertensive emergencies in children and to be as effective as nitroprusside in adults without the risk of cyanide toxicity.[13] Nicardipine is quite selective for the peripheral vasculature. It produces vasodilation of cerebral and coronary vessels with little effect on the heart, although there is a small chance of reduced heart rate. Thus, this medication is contraindicated in patients with advanced aortic stenosis and the manufacturer recommends caution in patients with heart failure and left ventricular dysfunction, especially when concomitant β-blockers are administered.[6] A few reports of reflex tachycardia do exist.[7] Propranolol has been used to treat reflex tachycardia, but caution must be used to avoid hypotension.[6] In contrast to labetalol, nicardipine may be safely used in patients with bronchospastic diseases.[7] There have been reports of thrombophlebitis when given through peripheral IV; if administering by this route, rotating sites every 12 hours may reduce the risk of thrombophlebitis.[13] The normal concentration for administration by peripheral IV is 0.1 mg/ml; higher concentrations up to 3.6 mg/ml have been given safely via central lines.[6] Another disadvantage of nicardipine is that it may cause an increase in intracranial and intraocular pressure; its use is thus discouraged in patients with suspected intracranial masses or space-occupying lesions.[7,13] Although no specific dosing recommendations exist for use in renal or hepatic failure, conservative doses are recommended.[6]

Fenoldopam

Fenoldopam is a dopamine D_1 receptor agonist that causes vasodilation of coronary, cerebral, renal and splanchnic vasculature, leading to a dose-dependent decrease in blood pressure.[7,9] It also has been associ-

ated with short-term increases in urine output and creatinine clearance.[13] There are some reports of reflex tachycardia with large doses; in some pediatric patients, the tachycardia lasted four hours or more.[6] Doses greater than 1.2 mcg/kg/min intravenously have been associated with greater tachycardia without greater hypotensive effect.[7] No dose adjustments are required in renal or hepatic dysfunction. Notably, the dosage range for fenoldopam in children is significantly higher than the adult range, suggesting that fenoldopam may have lower efficacy in children than in adults. There are reports of hypokalemia and increased intracranial and intraocular pressure in adults.[6,7,13] When used for longer than 48 hours, tolerance may develop.[13] In adults, fenoldopam was shown to have similar efficacy and safety as nitroprusside in the treatment of hypertensive crisis but was much more costly; however, fenoldopam has no risk of cyanide toxicity. Concomitant use with β-blockers should be avoided to reduce the chance of severe hypotension as β-blockers inhibit the sympathetic reflex response to fenoldopam.[6]

Enalaprilat

Enalaprilat is an angiotensin converting enzyme inhibitor (ACE-I) that is useful in renin-dependent hypertension.[7] Enalaprilat may be given by either IV push or intermittent infusion but is not appropriate for use in a continuous infusion.[6] Its use is contraindicated in patients with a history of angioedema due to ACE-Is and hereditary or idiopathic angioedema because anaphylactoid reactions requiring immediate airway management have occurred.[6] Enalaprilat can be difficult to titrate due to its slow, hour-long onset and extended duration.[15] This medication also has the potential to cause renal failure, especially in the neonate in whom the drug is eliminated more slowly and has an extended duration of action.[6,7] It requires dose adjustment in renal failure.[6] Clinicians should be aware that the formulation contains benzyl alcohol, which has been associated with the Gasping Syndrome (metabolic acidosis progressing to respiratory distress and gasping respirations). Transient hyperkalemia has been observed in adults.

Role of Pharmacists

Pharmacists can play an active role in both preventing and treating hypertensive emergencies in pediatrics. In the community setting, they can play a proactive role by counseling the parents of pediatric patients, especially those with hypertension, on the importance of adherence, possible drug interactions (especially with monoamine oxidase inhibitors) and other concerns with the different classes of drugs. For pediatric patients diagnosed with hypertension, the pharmacist can monitor blood pressure by performing blood pressure checks between physician appointments. The pharmacist should ensure the use of the proper cuff size to prevent errors in measurement. Pharmacists can also educate parents on poison prevention safety to avoid accidental ingestion of drugs that may cause hypertensive emergencies.

Health-system pharmacists can develop guidelines to facilitate optimal treatment of pediatric patients with hypertensive emergencies. They can take complete medication histories to identify drug-related causes of hypertensive emergencies and assist in the selection and modification of therapy. They should also ensure that proper weights, heights, and renal and hepatic function have been documented to ensure accurate dosing.[7]

Conclusion

Pediatric hypertension has become more prevalent within the last decade. There are many possible causes of hypertension in this population. Patients can present with hypertensive urgency or emergency, which are differentiated by the presence of acute end-organ dysfunction and are treated accordingly. There are many different agents used in the treatment of hypertensive emergencies with the majority of them being administered parenterally with a rapid onset of action and easy titration to prevent hypotension. The treatment of hypertensive emergencies in pediatric populations has not been extensively studied due to strict testing guidelines. This leaves a great deal of room for advancements in therapy options for pediatric hypertensive emergencies, as current treatment is generally guided by experience and expert consensus. Optimal treatment of children with hypertensive emergencies may be impaired by unfamiliarity with available agents and paucity of evidence on which to base clinical decisions. Pharmacists and other clinicians must be cognizant of the special issues involved in treating pediatric patients and familiar with best practices to ensure the safe and appropriate treatment of pediatric patients with severe hypertension.

Table 1: Common Medications for the Treatment of Pediatric Hypertensive Emergencies

Generic Drug Name	Mechanism of Action	Dose	Route	Onset of Action	Duration of Action
Sodium Nitroprusside[5,6]	Vasodilator	0.25-10 mcg/kg/min	Continuous IV infusion	Within seconds	1-10 min
Nitroglycerin[6,9]	Vasodilator	0.25-10 mcg/kg/min	Continuous IV infusion	1-5 min	5-10 min
Labetalol[5,6,9]	α_1 and non-selective β-adrenergic blocker	0.25-1 mg/kg/hr (bolus) or 0.25-3 mg/kg/hr (continuous)	IV bolus or continuous IV infusion	2-5 min	2-4 hr
Esmolol[4,9,12]	β_1 selective β-blocker	500-600 mcg/kg loading dose, then 100-500 mcg/kg/min	Continuous IV infusion	Immediate	10-30 min
Hydralazine[5,6,7]	Vasodilator	0.2-0.6 mg/kg every 4 hr	IV	5-30 min	2-6 hr
Nifedipine[5,11,14]	Calcium channel blocker	0.2-0.5 mg/kg/dose	Peroral	5-15 min	8 hr
Nicardipine[4-6,9]	Calcium channel blocker	1-5 mcg/kg/min	Continuous IV infusion	Within minutes	4-6 hr
Fenoldopam[6,7,9]	D1 receptor agonist	0.2-0.8 mcg/kg/min	Continuous IV infusion	5 min	30-60 min
Enalaprilat[6,7,15]	Angiotensin converting enzyme inhibitor	5-10 mcg/kg/dose	IV push or intermittent IV infusion	1 hr	24 hr

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Role of Non-nutritive Sweeteners in Obesity and Diabetes

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Abstract

Artificial sweeteners have become a central component of the Western diet in order to facilitate weight loss and enhance glucose control. Despite their popularity, evidence supporting the benefits of artificial sweeteners remains contradictory; different trials have shown weight loss, weight gain or no change with artificial sweetener consumption. Multiple trials have correlated artificial sweetener usage, in the form of diet soda, with an increased risk of obesity, diabetes and/or metabolic syndrome. Hypotheses speculate that individuals who consume larger loads of artificial sweeteners may be more likely to make unhealthy lifestyle choices, putting them at an increased risk for the development of these disease states. Although the link between artificial sweeteners and developing obesity or diabetes remains unclear, it is important for the general public and health care professionals to be aware of this potential relationship in order to make educated decisions about the foods and beverages they consume.

Introduction

The prevalence of both obesity and diabetes has increased over the past 30 years, as has the use of non-nutritive sweeteners (NNS). NNS are sugar substitutes the body does not metabolize; therefore, they do not provide calories or energy. NNS also are referred to as artificial sweeteners, high-intensity sweeteners, non-sucrose sweeteners, sugar substitutes or sugar-free sweeteners. The safety of NNS remains questionable due to possible obesity and diabetes links, yet more than 6,000 currently marketed food, medication and cosmetic products contain a mixture of the five FDA-approved NNS (table 1).[1] Contradicting evidence exists regarding the role of NNS use in obesity and diabetes. This article will outline the debate regarding the relationship of NNS to obesity and diabetes and discuss other related lifestyle implications.

Obesity

From 1960-80, obesity rates in the United States remained constant, with approximately 14 percent of the population classified as obese.[2] In 2000, this rate jumped to 31 percent, and figures from 2008 estimated 34 percent of Americans were obese.[3] Obesity is defined as a having a body mass index (BMI) of 30 or greater and occurs when more calories are consumed than the body uses.[4] People may find it easy to unconsciously consume a large amount of calories when drinking beverages and eating foods low in nutrients, such as soft drinks and snacks that frequently contain NNS. There are opposing thoughts about the use of NNS in relation to weight loss. Hypothetically, NNS may reduce caloric intake without sacrificing taste, promoting weight loss; however, there also is evidence that NNS use may result in weight gain.

Non-nutritive sweeteners do not contain calories but still sweeten foods and beverages, reducing the amount of calories consumed. The American Dietetic Association suggested if added sugars were replaced with NNS, an average of 380 fewer calories would be ingested per day, resulting in a weight loss of approximately one pound over 10 days.[1] Raben observed this possible correlation between NNS and weight loss in a randomized, blinded, parallel study of 41 healthy overweight individuals.[5] After 10 weeks of taking a NNS or sucrose supplement, the sucrose group gained 3.5 pounds, whereas the NNS group lost 2.2 pounds.

Alternatively, when NNS are added to a patient-controlled diet, the benefits of weight loss do not necessarily occur. Rodin conducted a randomized, patient-controlled experiment of 12 men and 12 women, including both overweight and normal weight individuals.[6] Thirty-eight minutes before eating a buffet meal, researchers gave participants 500 ml of either water or a beverage sweetened with fructose, aspartame or glucose and subsequently calculated the number of calories each person consumed. Regardless of the pre-meal beverage, overweight participants consumed more calories than those of a normal weight,

Table 1. FDA approved artificial sweeteners[1]

Type	Other Names	Relative Sweetness (to Sucrose)	Description	Regulatory Status
Sucralose	Splenda®	**600**	Most popular; produces no glycemic response	General-purpose sweetener
Acesulfame potassium	Sunett®	**200**	Second most popular; often used in combination with other sweeteners; produces no glycemic response	General-purpose sweetener
Aspartame	Equal®	**160-200**	Third most popular; metabolism yields phenylalanine; allergic reactions reported; limited glycemic response	General-purpose sweetener
Saccharin	Sweet'N Low®, Hermesetas	**200-700**	Often used in combination with other sweeteners: produces no glycemic response	Additive to foods and beverages, tabletop sugar substitute, also used in gum, cosmetics and pharmaceuticals
Neotame	Not currently available	**7,000-13,000**	Metabolism yields phenylalanine; produces no glycemic response	General-purpose sweetener

indicating obesity is a complex disorder. Individuals who drank water or aspartame beverages consumed a similar amount of calories but ate more than those who had fructose- or glucose-sweetened drinks. The study demonstrated that aspartame alone did not cause the consumption of more calories. When calories from the pre-meal drink and the meal were added, the totals were similar in all groups; therefore, the participants given aspartame or water compensated for calories not contained in the drink.

Lavin looked specifically at the total caloric intake of women over two days after drinking 330 ml of carbonated water, a drink containing aspartame, or a drink containing sucrose in a randomized, patient-controlled trial.[7] One week later, the women were given different beverages than the previous week, and the experiment was repeated. Participants consumed the beverage four times during the testing day; researchers measured all food eaten during the first day and relied on patients to self-report food eaten during the second day. The results showed no difference in the total amount of calories consumed on the first day when including the calories in the sucrose-sweetened beverage. Conversely, women who drank the aspartame-sweetened beverages consumed more calories during the second day, specifically in the form of carbohydrates. This study suggested that NNS may not be beneficial for weight loss because people tend to compensate for missing calories initially and actually eat more on subsequent days.

Diabetes

Non-nutritive sweeteners can be valuable to diabetic patients because they provide a sweet taste without sugar.[1] Grotz conducted a randomized, double-blind study in 128 subjects with type II diabetes that demonstrated the benefits of NNS in this population.[8] The results showed that sucralose consumption of 667 mg/day for 13 weeks had no effect on glycosylated hemoglobin (HbA1C), fasting plasma glucose, or fasting serum C-peptide. Based on individual body weight, daily sucralose consumption by participants in this study was calculated to be 7.5 ± 0.2 mg/kg/day, which is approximately three times higher than the estimated daily intake of 2.4 mg/kg/day. This study concluded that sucralose consumption of 7.5 mg/kg/day for 13 weeks had no effect on glucose homeostasis in type II diabetics, and sucralose-sweetened foods or beverages are beneficial for patients with diabetes.

Despite these positive findings, there are concerns that NNS use can increase the risk of developing type II diabetes and may be detrimental to people with diabetes. People with type II diabetes are at an increased risk for metabolic syndrome, defined as a group of cardiovascular risk factors including increased waist circumference, elevated blood pressure and insulin resistance.[9] Recent studies examined a possible link between NNS and the risk of developing diabetes. In the Multi-Ethnic Study of Atherosclerosis (MESA), diet soda consumption was evaluated by a food frequency questionnaire in 6,814 Caucasian, African American, Hispanic and Chinese adults aged 45-84 years. The study found that consumption of one or more servings of diet soda daily was associated with a 67 percent greater relative risk of developing type II diabetes and a 36 percent greater relative risk of developing two components of metabolic syndrome: high fasting glucose and increased waist circumference. The type of NNS used in diet soda manufacturing was variable throughout the study; therefore, results could not be attributed to one specific NNS. The study concluded that diet soda, either independently or in combination with other dietary and lifestyle behaviors, increased the risk of development of metabolic syndrome and type II diabetes.

In the Atherosclerosis Risk in Communities (ARIC) study, 9,514 participants, aged 45-64 years, were assessed using a food-frequency questionnaire at baseline and followed for a period of nine years.[10] Data collected at three-year intervals was used to evaluate the relationship between dietary intake and the development of metabolic syndrome. At the conclusion of the study, consumption of one serving of diet soda per day was associated with a 34 percent higher risk of metabolic syndrome. Mackenzie used data obtained in the third National Health and Nutrition Examination Survey (NHANES III) to examine the relationship between beverage consumption and glucose control in American adults with and without diabetes.[11] Diabetes status, glycosylated hemoglobin and a one-month recall food-frequency questionnaire were evaluated in 14,900 participants aged 18-75 years. The study found a correlation between diet soda consumption in adults with diabetes and poor glucose control, as measured by Hemoglobin A1C.

Lifestyle Choices

The development and progression of metabolic syndrome and type II diabetes also may be related to the consumption of soda. Dhingra examined the relationship between soft-drink consumption and metabolic syndrome in 6,039 Framingham Heart Study participants (mean age 52.9 years).[12] For inclusion, participants attended two consecutive examinations from 1987-2001 and reported the average number of 12-ounce servings of soft drinks consumed per day. This study concluded that the consumption of more than one soda per day, diet or regular, was associated with an increased incidence of multiple metabolic risk factors, indicating that the consumption of soft drinks, not necessarily NNS, is associated with metabolic syndrome and, possibly, diabetes. The researchers theorized that the intense sweetness of soft drinks may increase a person's preference for sweetened items and the consumption of soft drinks may be associated with other poor dietary and lifestyle behaviors.

In accordance with Dhingra's conclusion, other studies also have suggested that dietary and lifestyle choices may confound the relationship between artificial sweetener consumption and metabolic disease development. The authors of MESA speculated that artificial sweetener use may increase the desire for sweetness and energy-dense foods.[9] With diet soda consumption, overconsumption of other foods and beverages may result based on overestimation of the number of calories saved by substituting diet for sugar-sweetened beverages. An analysis of the NHANES III data suggested that consumption of diet beverages is more likely in those patients who have a tendency towards poor glucose control.[11]

Conclusion

A correlation exists between the use of NNS and the development of obesity and diabetes; however, many other factors, such as soda consumption, also could play a role. NNS are not the sole cause of the current obesity and diabetes epidemics, but they may be a contributing factor to the increasing prevalence of these diseases over the past 30 years. As with any healthy diet, moderation is imperative. It is important for the general public and health care professionals to be aware of the potential relationship between NNS and both obesity and diabetes in order to make educated decisions about the foods and beverages they consume.

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Polycystic Ovarian Syndrome and Hyperinsulinemia: Overview and Treatment

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Abstract

Polycystic ovary syndrome is a prevalent issue in women's health that is associated with hyperinsulinemia and insulin resistance and can lead to long-term health problems. The most highly recommended treatments are diet and lifestyle changes. If these changes alone are not enough, pharmacologic treatments may be employed, which include metformin, spironolactone or thiazolidinediones, although more research is needed to fully realize their role. The role of the pharmacist in this disease state includes counseling patients on healthy lifestyle changes, consulting with the physician about prescribing the best medication for each patient, and monitoring therapy adherence in the patient.

Introduction

Polycystic ovarian syndrome (PCOS) is a prevalent disorder affecting 6-15 percent of women of reproductive age.[1] PCOS is a pleiotropic syndrome that can have deleterious effects on the entire body. Hyperinsulinemia is one of the main concerns associated with this syndrome because it can increase the risk for many other disease states in a woman with PCOS. There are few treatment options for PCOS at this time; but by understanding the safety and efficacy of the available options, pharmacists can help their patients better understand the disease state and medications. Pharmacists can further take an active role by providing screenings and educating patients on preventative measures for women who are at risk of developing this disease.

PCOS

Polycystic ovarian syndrome is the most common endocrine disorder among premenopausal women.[1] The symptoms of this disorder are varied and extend beyond reproductive system problems. Along with menstrual irregularities, chronic anovulation and possible infertility, women with PCOS often develop hirsutism, acne, hyperandrogenism and inappropriate gonadotropin secretion.[1-4] While some of the symptoms may only be frustrating or uncomfortable for the patient, a woman with PCOS is at risk for developing other conditions that are not as benign. A PCOS diagnosis means the patient is at an increased risk for insulin resistance, hyperinsulinemia, dyslipidemia, hypertension, gestational and type 2 diabetes, systemic inflammation, endothelial dysfunction, and cardiac events such as myocardial infarction or cerebral vascular accident.[5] Although PCOS is a common problem, its pathogenesis remains unknown. It is not merely a structural disorder; rather, it has definite ties to problems with hormones, genetics, and even potentially altered central nervous system (CNS) function.[6] There are theories that PCOS has a genetic component due to a gene mutation in ovarian and adrenal androgen synthesis as evidenced by a higher incidence of PCOS among first-degree relatives. CNS problems such as epilepsy and bipolar disorder may also play a role in PCOS but more research needs to be done before a more concrete conclusion is reached regarding this potential relationship.

Hyperinsulinemia

Hyperinsulinemia and insulin resistance are commonly associated with PCOS. Hyperinsulinemia increases production of already elevated androgens, worsening PCOS symptoms. This is accomplished by overproduction of ovarian androstenedione and adrenal dehydroepiandrosterone (DHEA), which leads to excess estrogen in the periphery. Elevated estrogen increases the ratio of luteinizing hormone (LH) secreted by the anterior pituitary gland to secretion of follicle stimulating hormone (FSH).[1] Increased LH secretions lead to amenorrhea, infertility, anovulation and hyperandrogenism.

The hypothalamic-pituitary axis also is affected by excess release of adrenocorticotropic hormone (ACTH) in response to corticotropin-releasing hormone (CRH).[1] ACTH stimulates lipoprotein uptake by cortical cells, which can lead to higher cholesterol levels. This dysregulation of cholesterol levels correlates to the finding that many women with PCOS are obese. Hyperinsulinemia also may possibly contribute to this weight gain. Overall, insulin resistance and compensatory hyperinsulinemia are contributing factors for anovulation, hyperandrogenism, infertility and early pregnancy loss associated with PCOS patients (Figure 1).

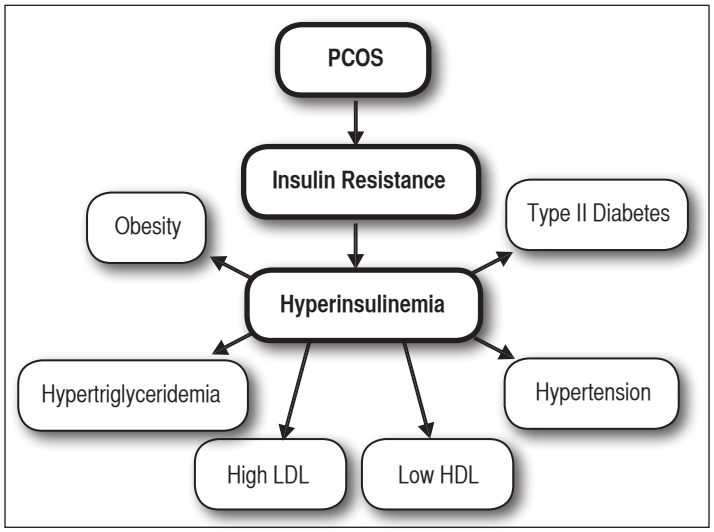

Figure 1. Detrimental effects of PCOS-induced hyperinsulinemia

Non-pharmacologic Treatment Options

The most highly recommended way to treat PCOS is altering the diet to include healthier options, such as whole grains and fresh produce, and reduce the intake of highly processed foods and foods high in fat or sodium. Incorporating exercise into daily life also is recommended.[7] Eating foods that help decrease LDLs and increase HDLs, such as high fiber foods and foods containing omega-3 fatty acids (fish and nuts), can be beneficial dietary modifications.[8] Achieving ideal body weight and exercising at least five times per week can potentially alleviate many symptoms associated with PCOS as well as reverse the progression of concurrent disease states.

A diet that has recently received significant media and patient attention is the human chorionic gonadotropin (hCG) diet. Human chorionic gonadotropin is a hormone produced by the trophoblastic cells of the placenta during pregnancy.[9] The hCG diet supposedly mobilizes fat stored in the abdomen, hips and thighs while keeping the patient feeling satiated. The diet involves three "gorging days," to build up calories in the body, followed by a strict, very low-calorie diet of 500 calories a day while receiving hCG as injections, sublingual drops or lozenges. Despite some clinical trials showing benefits, the FDA denies that hCG has any benefit in treating obesity.[10] Currently, the only FDA-approved use for hCG is for fertility treatment.[11] The diet is not recommended for weight loss in most patients, but it may be used as a last resort for patients who desperately need to lose weight. Pharmacists can counsel patients about the risks associated with the diet, monitor its correct use and ensure the safety of the patients.

Pharmacologic Treatment Options

There are limited pharmaceutical options that can be utilized; however, because of the underlying problem with hyperinsulinemia, insulin-sensitizing agents may be beneficial in treating PCOS.[12] The three products that currently are used in the treatment of PCOS are metformin, spironolactone and thiazolidinediones (TZDs). These medications all have different mechanisms of action and treat PCOS in a variety of ways. Further resesarch is necessary prior to widespread use of these agents.

Metformin is a commonly used and studied treatment of PCOS in patients with hyperinsulinemia. There are various potential mechanisms by which metformin may lower insulin levels, including the inhibition of gluconeogenic enzymes, reduced uptake of enzymes needed for hepatic gluconeogensis, increased phosphorylation of insulin receptor and insulin receptor substrates, and inhibition of mitochondrial respiration, which can reduce the energy supply needed for gluconeogenesis.[13] In patients with PCOS, the lowering of insulin levels can lead to improved ovarian function as well as improved glucose metabolism.[14] Lowering insulin levels also may reverse the dysfunction in the hypothalamic-pituitary-ovarian axis, causing a decrease in androgen levels.[13] Additionally, metformin has effects on free fatty acid synthesis, which indirectly lowers gluconeogenesis activity. It does this through antagonism of acetyl-CoA carboxylase activity so that there is decreased fatty acid synthesis and increased mitochondrial fatty acid oxidation. These two effects on the body lead to a reduction in hepatic lipid levels and lowered plasma triglyceride levels. While the effects of metformin seem to be beneficial in women with PCOS, there are side effects to consider that may deter patient use of this medication. The most common issues are gastrointestinal-related, such as nausea, vomiting and diarrhea.[15] These are typically resolved in a few days or weeks and can be minimized by taking metformin with meals and following a gradual titration schedule.[13] A change in diet and exercise patterns, along with the use of metformin, can improve cardiometabolic irregularities and may even restore ovarian function.

Spironolactone is another treatment option for women with PCOS. Along with diuretic properties, spironolactone may be used as an antiandrogen for female hirsutism. Though the mechanism is unknown, it is thought to block androgen receptors and may decrease the overall production.[3] According to a randomized, open-label study of 69 PCOS patients comparing spironolactone and metformin treatment, there was no significant effect on BMI, waist-to-hip ratio, blood pressure, oral glucose tolerance test parameters or insulin sensitivity when patients received a 50 mg/day dose of spironolactone.[16] However, there was a significant improvement in menstruation cycle, hirsutism and androgen levels. While spironolactone was superior in helping with hirsutism and patient acceptance, metformin was more effective at improving glucose tolerance and insulin sensitivity. Although spironolactone is an option in the treatment of PCOS, it is not preferred because it does not cause significant improvement in glucose tolerance and insulin sensitivity.

Another pharmacologic option is a TZD such as rosiglitazone or pioglitazone. Both of these drugs are agonists of the peroxisome-proliferator-activated receptors (PPARs), which, when activated, influence the production of proteins involved in glucose and lipid metabolism.[15] This improves response to insulin without influencing the amount of insulin that is secreted by the pancreas. In a randomized, two-armed, head-to-head study of 96 patients, it was found that rosiglitazone was more effective than metformin at reducing female hirsutism, but it was not found to be more beneficial at reducing insulin levels, even though there was a significant reduction in fasting insulin levels in the use of rosiglitazone.[2] Although these results sound promising, due to a recent change in the FDA Black Box Warning regarding increased risk of cardiac events, rosiglitazone should not be used in PCOS patients because they are predisposed to such events.

Pioglitazone has also been studied in the treatment of PCOS. A randomized controlled trial of 52 patients found that a six-month administration of pioglitazone in obese women was as effective as metformin in reducing fasting insulin levels without drastically changing glucose concentration.[17] There also was a significant reduction in hirsutism and serum concentrations of testosterone and androgens. Pioglitazone use may cause an increased risk of bladder cancer as indicated by the FDA Black Box Warning. This risk should be taken into consideration when choosing a treatment, and patients should be monitored. Due to the Black Box warnings, and because there's no significant benefit over metformin or spironolactone, the use of TZDs in women with PCOS is not recommended as a first choice of therapy in the treatment of PCOS.

Conclusion

Pharmacists can assume an active role when assisting with the treatment of hyperinsulinemia in PCOS. Awareness of the treatment options available can allow pharmacists to ensure that prescribers are utilizing the optimum treatment plan for the patient. Metformin is generally the first-choice option in the treatment of hyperinsulinemia in PCOS. Since there are several negative side effects associated with the drug, the pharmacist can communicate with the prescriber about a titration schedule in order to make the patient more comfortable. Spironolactone is not as effective as metformin in treating hyperinsulinemia, but it does treat the problems caused by excess androgens. TZDs are not recommended in the treatment of PCOS because of the Black Box warnings and concerns of patient safety; however, patients already taking a TZD should be counseled on correct and safe use. Aside from counseling the patients on their prescribed medications, pharmacists can help with screenings to track patient progress. Such screenings include glucose screenings, lipid panel screenings, and body mass index values. Becoming involved in the outpatient setting can allow pharmacists to alert patients to any concerning lab values or assist patients with plans and

tracking of lifestyle changes. Because of the complexity of PCOS, it is important to treat each patient based on individual symptoms and needs. Due to the accessibility of pharmacists, counseling PCOS patients is a positive opportunity to take on an integral role in helping patients manage and improve the symptoms of this disease state.

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Prevention of Cytomegalovirus Infection in Pregnant Mothers and Neonates

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Abstract
Congenital cytomegalovirus (CMV) is the most common virus spread in utero from mother to fetus, leading to more long-term problems and childhood deaths than other conditions such as Down syndrome, fetal alcohol syndrome, pediatric HIV/AIDS, or neural tube defects. The majority of congenital CMV infections are primary infections in which the mother acquires the infection during pregnancy. Current treatment options for CMV infection are available, but there is limited data on safety and effectiveness in pregnant mothers and neonates. Prevention by screening for CMV is associated with a high cost, and vaccines are currently unavailable. Studies show that education and behavioral modifications are effective ways to lower the risk of CMV infection in neonates, making primary prevention by these methods critical to reducing the transmission of CMV infection.

Overview

Cytomegalovirus is the most common virus spread in utero from mother to fetus within the U.S. Every year, approximately 30,000 infants are born within the U.S. with congenital cytomegalovirus (CMV). Eighty percent of these infants will be asymptomatic, but the remaining infants will likely develop neurologic sequelae, equating to more than 5,000 children each year who are born with or develop permanent disabilities and approximately 400 deaths due to CMV.[1,2] CMV leads to more long-term problems and childhood deaths than other conditions such as Down syndrome, fetal alcohol syndrome, pediatric HIV/AIDS, or neural tube defects. Unfortunately, only 14-22 percent of women are aware of CMV, and fewer than half of obstetricians talk to expectant mothers about the virus.[1,3] A member of the herpes virus family, CMV lives within its host for the duration of the host's lifetime, although its activity is usually dormant.[4]

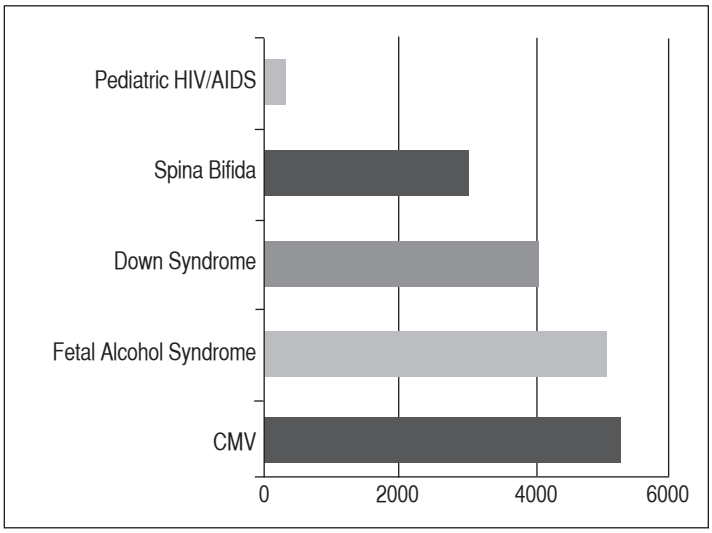

Figure 1. U.S. Children Born with or Developing Long-Term Medical Conditions Each Year[1] (Adapted from CDC.gov)

An estimated 60 percent of women of child-bearing age in the U.S. are infected with CMV.[5] Of the remaining 40 percent of women who have never been infected with CMV, approximately 1-4 percent will acquire a primary infection while pregnant.[1] A mother acquires CMV by coming into contact with urine, saliva or genital secretions of an infected person.[5] Seronegative mothers with a CMV-infected child typically become infected within one year after their child acquires a CMV infection, and up to 70 percent of children in group childcare acquire CMV.[6] CMV infection can occur one of two ways during pregnancy: The mother can either receive a primary infection, in which the mother acquires the virus during pregnancy, or the infection can result from a secondary infection in which a dormant virus reactivates. Primary infections are the cause for the majority of infants who are born with a congenital CMV infection, and secondary infections account for only about 2 percent of congenital CMV infections.[7] Women can infect the fetus during any trimester or perinatally via contact with genital secretions at birth and/or from breast milk.[5]

A majority of children born with congenital CMV never experience any problems or symptoms, but about one in every 750 children born with CMV suffer from permanent problems due to the infection. Short-term effects of congenital CMV infection include premature birth, hepatomegaly, splenomegaly, jaundice, purpura, petechia, pneumonitis and seizures. Permanent outcomes consist of microcephaly, vision loss, hearing loss, learning disabilities, motor disabilities, seizures, cerebral palsy and, in some cases, death.[1,8,9] Almost all adults have been exposed to CMV, but a healthy adult with a normal immune system will likely be asymptomatic. Those at increased risk for infection include babies born to women who have a first-time CMV infection during pregnancy, pregnant women who work with infants and children, and persons with weakened immune systems.[10] Hearing and vision loss may not develop until one to two years after birth, so the Centers for Disease Control and Prevention (CDC, Atlanta, Ga.) recommend that seropositive, asymptomatic children have their hearing and vision monitored regularly. It is estimated that one-third of sensorineural hearing loss in children is due to CMV infection.[9]

Screening

Currently, there are no systematic screening programs in place to identify patients in at-risk groups so that educational programs can be tailored to patient's specific test results, allowing for appropriate primary, secondary and tertiary prevention methods and behavior modification. A screening program offered at the beginning of pregnancy could identify women who are seronegative and provide an opportunity for primary prevention strategies such as education and behavior modification to prevent seroconversion during pregnancy.[7] Screening at the start of pregnancy uses serological tests of urine, saliva or tissue samples to identify CMV IgG and IgM antibodies. The presence of antibodies indicates CMV infection but cannot identify whether an infection is primary or recurrent. This may cause unnecessary patient anxiety because primary infections are more likely to cause complications than recurrent

infections.[11] If a mother has already seroconverted, additional screenings which use ultrasound can identify fetuses that express cerebral complications, allowing secondary prevention strategies to be implemented with a goal of preventing complications due to infection. Ultrasound screening after mother seroconversion is not very effective because most fetal defects cannot be identified until the last trimester. Screening methods also can be used to target tertiary prevention strategies such as early management of neurological sequelae. One method of tertiary screening is to use serological tests at the beginning and throughout pregnancy to give a prenatal diagnosis of the infant. Another method of screening is to perform a serological test of urine or dried bloodspots upon birth to identify asymptomatic infants. By identifying asymptomatic infants at birth that are seropositive, closer monitoring of neurological development can help manage subsequent sequelae that may not develop until later in infancy. Also, early identification of hearing loss through routine screening at birth may improve the prognosis for children with CMV. Testing of dried bloodspots could easily be incorporated into state newborn screening programs, which are already in place; however, dried blood tests are not as sensitive as urine tests. Limitations of tertiary prevention include minimal benefits for infants with severe neural complications and the lack of programs currently in place for continuing the monitoring of seropositive infants to help identify and manage potential complications. A major drawback to all types of screening is the cost associated with testing all pregnant women and neonates.[7,12]

Treatment

Current treatments for CMV are lacking safety profiles in pregnant women due to severe side effects and have no proven efficacy in preventing transmission to the fetus. Ganciclovir is a treatment option for congenital CMV infection but is limited to only the most severe cases due to its adverse event profile. It is an anti-viral agent that is used in an attempt to prevent hearing loss in infants. In a randomized, controlled trial, patients who received ganciclovir did not have any further hearing deterioration at six months; 41 percent of patients not receiving ganciclovir therapy demonstrated hearing deterioration (adjusted $P < 0.01$). However, the majority of patients who received ganciclovir therapy experienced significant hematological toxicity. Furthermore, its long-term safety has not been established in children.[13]

Another treatment option being explored is intravenous human immunoglobulin (IVIG) administration, but it is not currently approved for use in the treatment of CMV. Limitations in implementing IVIG therapy include a limited supply and cost of treatment.[6,14] Immunoglobulin therapy is still being studied in clinical trials and has emerged as an off-label use for CMV among physicians, but little is known about its toxicity.

Prevention

A vaccine is the most promising way to fight congenital CMV; however, a vaccine is not yet commercially available in the U.S.[5,8] It is estimated that with proper funding, a vaccine could be developed within seven years.[2] A vaccine could be given in childhood or adolescence, and prior immunization could prevent a primary CMV infection in women during pregnancy.[5] By implementing vaccination, it is estimated that approximately $4 billion in health care costs could be saved every year.[2] There currently are several vaccines in development.[5] Novartis and AlphaVax currently are developing a single-cycle particle vaccine that carries RNA encoding three antigens from the CMV virus. The vaccine will target adolescent women.[15] Sanofi Pasteur recently finished phase II trials of a molecule similar to Novartis' and found that the vaccine decreased the incidence of maternal and congenital CMV infection (no P value provided).[16] Vical also is developing a CMV vaccine, CyMVectin™, to prevent seroconversion prior to pregnancy. CyMVectin is set to enter phase I trials with the approval of their Investigational New Drug Application.[17] The biggest limitation in vaccine implementation is that several studies have shown that a previously infected person can become re-infected with a new strain of the virus, thus decreasing the likelihood that a single protein can provide immunity for all strains of the virus.[18]

Because vaccines are currently unavailable and treatment strategies are lacking safety profiles, education on preventing the disease through behavior modification is critical in preventing the transmission of the virus and subsequent infection in neonates. [6]

The American College of Obstetrics and Gynecology recommends counseling about CMV prevention by emphasizing hygienic practices.[8] There are many preventative strategies that can be employed by the patient to reduce the risks of acquiring or transmitting the disease. Both protective and avoidance behaviors need to be taught in the prevention against CMV (Table 1). Protective behaviors include frequent hand-washing after diaper changes, feeding or bathing a child, and handling children's toys as well as using gloves when cleaning surfaces that come in contact with saliva or urine. Avoidance behaviors include eliminating salivary contact by not sharing food, toothbrushes, utensils or pacifiers. Horizontal transmission of CMV is very common in childcare settings due to the high incidence of children under 30 months who actively shed CMV in their urine and saliva. Contact in the day-care setting can increase the risk of acquiring CMV by up to 25 fold.[9] It is estimated that those exposures can cause up to 12,000 cases of newborn infections and neurologic damage.[19]

Table 1: Behavior modifications to prevent transmission of CMV[1,8]

Ways to Reduce CMV Transmission
Wash hands thoroughly with warm soap and water • After diaper changes • After feeding or bathing the child • After wiping a runny nose or drool • After handling children's toys
Clean surfaces that come into contact with the child • Countertops • Toys • Surfaces in contact with urine and saliva
Limit sharing of objects in contact with saliva and/or urine • Cups • Utensils • Food • Plates • Toothbrushes • Towels and washcloths
Do not kiss on or near the mouth
Adults should not put a child's pacifier in their mouth

A study was conducted to test the efficacy of preventative methods in child-to-mother transmission of CMV in pregnant and non-pregnant mothers with children enrolled at 124 day-care centers in Virginia from 1999 to 2001. The women were randomized into three groups: a control group, a partial intervention group and a full intervention group. For all three groups, the women, all children in the home and the fathers had urine and saliva collected every three months for CMV screening for a total of 12 months or until delivery. The control group was only given basic information about CMV, and seroconversion results were not revealed. The partial intervention group was given information about the virus as well as a video presentation that focused on how to prevent transmission. This group was also taught about protective behaviors such as proper handwashing, wearing gloves when changing a diaper, and avoiding salivary contact with children through either sharing food and drink or kissing on the mouth. Latex gloves were given to the mothers to use during diaper changes as well as liquid soap. This group also underwent CMV screening, but only the mother's initial serum status was revealed. The full intervention group was given all of the same educational information, as well as prevention measures, given to the partial intervention group. The full intervention group also received CMV culture screening every three months but were told the initial results of the mother's and the child's screening. If a child was not shedding at enrollment, mothers were educated that there was a high probability their child could begin shedding the virus at any time. An interim analysis showed that half of the children who initially were not shedding began to shed the virus at some point during the study; therefore, all mothers enrolled in the partial intervention group were re-assigned to the full intervention group. The results of this study found that intervention in pregnant women may have lowered the risk of acquiring CMV by as much as 85 percent. Pregnant women were more motivated to incorporate the interventions into their daily lives. The women were more attentive, took notes and asked questions compared to their non-pregnant counterparts who seemed less engaged.[6]

Role of pharmacists

Due to the high financial costs and limitations associated with screenings and the lack of an effective and safe treatment option, the focus of health care providers must be on prevention when educating the patients about CMV. Health care providers can play an important role by raising awareness of CMV and educating the public about CMV, the risks associated with it and prevention of CMV transmission. Pharmacists can have a significant impact in creating awareness about CMV by educating women who are pregnant, planning on becoming pregnant or who have young children. The education can be delivered through materials such as pamphlets and videos, one-on-one counseling in a health care setting, or outreach programs.

Conclusion

CMV is the most commonly transmitted virus in utero and can have significant effects in a neonate. Because only 14-22 percent of women are aware of CMV, it is very important that health care providers become more proactive in educating patients and the general public, especially women of child-bearing age.[1] Pharmacists can play a key role in patient education on congenital CMV infection prevention. Studies have shown that education and behavioral modifications are effective ways to lower the risk of CMV infection in neonates, making primary prevention critical to reducing the transmission of CMV infection.

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Management of Breakthrough Pain in Cancer Patients: Traditional and Novel Approaches

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Abstract

Approximately 80 percent of cancer patients experience breakthrough pain (BTP) characterized by acute onset, short duration, and moderate-to-severe intensity. Treatment of BTP using current available medications is often insufficient, leading to the development of various novel approaches that focus on rapid onset of action and short duration of action. Most of these products are still in clinical trials, and future studies are needed to compare the novel approaches to currently available treatments. Non-medication related issues, which arise from a lack of communication and understanding between the patient, physician and pharmacist, are also barriers to adequate BTP management. By educating patients and working with physicians, pharmacists can play a major role in effectively managing cancer-related BTP.

Introduction

Cancer-associated pain is a serious clinical concern for patients and caregivers. It is a common occurrence in many cancer types and can be caused by both the disease and the treatment. It is important for health care professionals and patients to understand that there are two kinds of cancer pain that need to be managed: chronic baseline pain and breakthrough pain (BTP). The World Health Organization states that 90 percent of patients achieve adequate relief of chronic pain from relatively simple drug therapies.[1] Unfortunately, even when this baseline pain is managed effectively, instances of BTP still occur in upwards of 80 percent of patients.[2] The specific clinical features of BTP vary among individuals but are characterized by acute onset, short duration, and moderate-to-severe intensity. A 2008 study showed the median number of BTP episodes per day was two with a range of one to 10, and the median duration of each event was 30 minutes with a range of five seconds to 360 minutes.[2] Because traditional treatment of BTP in cancer patients is complex and often insufficient, various novel approaches are being studied.

Traditional Treatment

BTP is traditionally managed with oral immediate-release (IR) opioids. These are taken as needed in addition to regularly scheduled analgesics for chronic pain management. However, oral IR opioids are not an ideal choice because of delayed onset (average onset of action is 30-40 minutes) and a longer duration of action than needed for most BTP episodes.[3] When patients believe their rescue medication is taking effect, it may actually be the result of the BTP episode resolving on its own. Patients also may believe that they need to take additional doses of their medication when they do not experience rapid pain relief; in reality, their initial dose most likely has not yet taken effect. An ideal medication for the treatment of BTP would have a more rapid onset of action and shorter duration of action than those currently used.

Novel Approaches

Alternate routes of opioid administration may be able to achieve greater efficacy in managing BTP. Various transbuccal, sublingual and intranasal products can offer better bioavailability, quicker onset of action, and shorter elimination half-lives. While some of these opioids are currently available, others are still in clinical trials.

Transbuccal

Transbuccal administration of medications occurs via the transmucosal route often behind the rear molar, between the upper cheek and gum. Transbuccal medications with a labeled indication for BTP include fentanyl buccal tablets (FBT), oral transmucosal fentanyl citrate (OTFC) lozenges, and fentanyl buccal soluble film (FBSF).[4] These transbuccal dosage forms allow for increased bioavailability in comparison with traditional forms of opioid treatment, with an onset of action five to 15 minutes after administration. A 2007 study by Darwish et al. indicated that FBT resulted in higher early systemic exposure and higher peak concentrations at the same dosage strength as OTFC lozenges (t_{max}= 46.8 min and C_{max}=1.02 ng/mL vs. t_{max}= 90.8 min and C_{max}=0.94 ng/mL, respectively).[5] In addition, Vasisht et al. demonstrated that FBSF achieved greater plasma concentrations in roughly the same amount of time as OTFC lozenges ($p = 0.03$).[6] In a separate study also conducted by Vasisht et al., the bioavailability and transmucosal absorption of fentanyl via both FBSF and FBT were significantly higher when compared to oral administration, i.e. following the buccal doses, mean C_{max} and AUC_{inf} were 1.9 and 2.0 times that of oral administration.[7] While FBSF and FBT have shown quicker time to onset and better efficacy than OTFC, it is important to note that all three dosage forms have been statistically significant in decreasing the frequency and intensity of BTP in comparison to placebo in each of their respective studies.

Sublingual

The development of a sublingual dosage form was intended to potentially exploit a more rapid onset of action compared to other transmucosal opioid formulations. A double-blind, cross-over trial by Lannernas et al. studied the pharmacokinetics of three fentanyl sublingual tablet dosage strengths, 100 µg, 200 µg, and 400 µg.[8] Time to first detectable plasma concentrations (t_{first}) for all doses ranged from eight to 11 minutes and time to peak concentrations (t_{max}) varied from 45-60 minutes with a statistical non-significant increase in t_{max} in correlation to increasing dosage strengths (p=0.19-0.57). A single case study by Kunz et al. utilizing a more potent analogue of fentanyl, sufentanil, was found to provide "satisfactory" analgesia of BTP with 25 µg doses every three minutes (max dose of 75 µg).[9] The rapid onset of action of these sublingual products is promising; however, further studies need to be done in a larger patient population comparing these to traditional treatments and the other novel approaches.

Intranasal

The absorption of morphine, fentanyl, sufentanil or ketamine via the nasal cavity have all been assessed in clinical trials for BTP management. Pavis et al. studied an intranasal morphine-chitosan formulation that was found to have a duration of action of five to 45 minutes and to be effective (receiving a score of 1, or slight pain, on a 0-4 pain scale) in the relief of BTP at doses varying from 5-80 mg.[10] A randomized, double-blind, crossover study of fentanyl pectin nasal spray (FPNS) conducted by Portenoy et al. found the treatment to be "proven safe, well tolerated, and rapidly efficacious," improving mean summed pain intensity difference from 10 min ($P < 0.05$) until 60 min ($P < 0.0001$) in comparison with placebo using a 10-point pain scale.[11] Intranasal sufentanil also has been proven successful in the treatment of BTP. Good et al. reported a significant reduction in pain scores at 15 ($P < 0.0001$) and 30 minutes ($P < 0.0001$) in a prospective, open-label, observational study of 30 patients.[12] Currently entering phase III clinical trials is PMI-150 (intranasal ketamine) for the treatment of BTP in cancer patients. While other studies have assessed ketamine and determined its use sufficient in the treatment of BTP postoperatively, its effect on BTP in cancer patients never has been studied until now.[13] As with the other novel approaches, the intranasal medications show promise, but additional studies need to be performed to provide further support for their use in place of traditional treatments.

Challenges

The primary challenges associated with the use of these novel agents include observable side effects, dose titration of opioid treatment, availability, and cost. While these medications are short-acting, they still share a similar side effect profile of traditional opioids, including nausea, vomiting, constipation, dizziness and/or drowsiness.[1] Additional side effects associated with their respective route of administration have been observed. For example, intranasal irritation has been associated with the intranasal route of administration.[10] Another challenge is titration to a patient-specific effective dose. An effective dose is rarely achieved on the first attempt, as a result of the limited data available for the use of these agents, but is obtainable after a few administrations. With exception of the transbuccal opioids, the novel agents discussed are still in clinical trials and are not available for public use. The transbuccal opioids that are available are costly. Twenty 400 µg generic OTFC lozenges cost $400, and 28 200 µg Fentora® FBTs cost $660 in comparison to a traditional oral cancer pain agent such as 30 5-500 mg hydrocodone/acetaminophen tablets at $12.[4] Until these issues can be resolved, BTP will remain a difficult element of cancer treatment, leaving patients seeking answers from health care providers.

Discussion

Other challenges in the management of BTP are independent of the medications. These arise from a lack of communication and understanding between the patient, physician and pharmacist. Davies et al. found that 48 percent of patients cited an inappropriate reason as a primary or secondary concern for why they were not taking their prescribed breakthrough medication. These reasons include apprehension about adverse effects, the possibility of becoming physically dependent, or the possibility of becoming psychologically dependent.[2] Ensuring that patients truly understand the risks and have adequate opportunity to voice concerns is paramount to effective pain management. Furthermore, some physicians neglect to recognize the effect BTP may have on a patient and may place restrictions on how often an emergency dose can be taken. The same study mentioned above concluded that only 44 percent of patients were told they could take rescue medications as needed, and 15 percent were told they could not take the medications more than three times a day. This led to 80 percent of the patients using non-pharmaceutical methods to manage BTP. These methods included resting, exercising, application of heat, changing position and consumption of alcohol. Pharmacists have the opportunity to play a significant role by taking time to counsel patients about their pain medications and the management of their symptoms. As new and unique treatments become available, it will become even more important for the physician, pharmacist and patient to communicate and work together to develop the best pain management plan for each individual.

As the most accessible health care provider to patients, it is important for pharmacists to understand the reality of BTP and the current treatments available as well as those in development. A pharmacist's ability to identify this phenomenon within community, hospital, and palliative care settings is essential to maximize patient treatment outcome. By recognizing these instances of BTP, patients can be directed to their physicians for optimal treatment. Pharmacists can aid physicians in the accurate direction of BTP treatment by providing information about novel agents. While there is an obvious need for better treatment options for cancer-related BTP, further studies need to be conducted regarding the use of the novel approaches before they will significantly change clinical practice. Studies comparing these products to traditional treatments, rather than placebo or themselves, also will be necessary.

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Fentanyl: Abuse Potential and Prevention Strategies for Pharmacists

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Abstract
The abuse of fentanyl is becoming more prevalent, with patients devising new methods of extraction in order to abuse it. Fentanyl patches were originally intended for the opioid tolerant patients still requiring pain relief, but illicit use and drug diversion of this medication continues to grow at an alarming rate. Several cases of abuse have been documented in which patients were chewing patches for oral absorption, distilling the drug into liquid form for injection, or rectally inserting the patches. To discourage and prevent abuse, a keenly aware pharmacist can provide patients with important counseling points on proper use, disposal and education about fentanyl itself.

Background

Fentanyl patches are prescribed for the treatment of persistent, moderate-to-severe chronic pain. This drug therapy is reserved for patients who are opioid tolerant; however, due to its euphoria-inducing properties, fentanyl has a high potential for abuse. While fentanyl is less commonly abused than medications such as oxycodone or hydrocodone, abuse has increased in the last decade, with widespread epidemics occurring in cities such as Chicago, Detroit and Philadelphia.[2-4] In 2006, fentanyl was the fifth most common cause of emergency department visits resulting from nonmedical prescription narcotic analgesics.[5] Due to the prevalence of abuse and severe consequences of misuse, there is a definite need for intervention and patient education on the safe use of transdermal patches.

Fentanyl acts systemically as a mu-opioid receptor agonist (table 1) and has the capability to cross the blood-brain barrier due to its highly lipophilic nature, which results in analgesic effects, mood alterations, euphoria, dysphoria and drowsiness.[1] The high potency of fentanyl allows for a therapeutic dose to be applied to a relatively small area of skin. Chronic opioid users frequently develop tolerance to the analgesic and euphoric effects, but not to the respiratory depressive effects. Toxicity can range from mild, which presents with drowsiness and headache, to severe which may result in respiratory arrest, hypotension and even death. Adverse effects of the transdermal application include nausea, vomiting, confusion, skin irritation and insomnia.

Table 1: Systemic effects of fentanyl by opioid receptor type[1]

Opioid receptor	Systemic effects
Mu	Supraspinal and peripheral analgesia, sedation, and euphoria Spinal analgesia, respiratory depression, physical dependence, GI dysmotility, bradycardia, pruritus
Kappa	Spinal analgesia and miosis Dysphoria and psychotomimesis Supraspinal analgesia

As an attempt to deter abuse, a novel matrix delivery system was more recently introduced.[6] The new patch is smaller, with fentanyl-containing dipropylene glycol droplets incorporated into the adhesive rather than the original reservoir system, which is known to leak drug and allows for simple drug extraction. The matrix delivery system has a rate-controlling membrane to improve drug release, which allows the amount of drug loaded in the patch to be reduced by almost 35 percent compared to that contained in the original reservoir system. Since fentanyl is completely dissolved in a semisolid state in the matrix formulation, the risk of incidental drug leakage is decreased. Extraction of drug for abuse was thought to be more difficult, though it has now been shown to be just as commonly abused as the original reservoir patches.[7]

Methods of Abuse

Abuse of transdermal fentanyl patches involves unintended routes of administration achieved by altering the delivery system. In situations of abuse, fentanyl may be introduced by transmucosal application, ingestion, intravenous injection of the patch contents, volatilization and inhalation, application of heat to a transdermal patch, or rectal insertion.[8,9] While the patches are intended for slow, steady drug release, these rapid infusion methods result in uncontrolled quantities of drug delivered.[8] Moreover, fentanyl is frequently abused in conjunction with alcohol or other illicit drugs, even acting as a substitute for heroin.[9]

The most popular method of abuse involves placement of a transdermal fentanyl patch inside the oral cavity.[8,9] Oral abusers will affix a patch, or patches, on the buccal membrane, chew on the patch, or boil the patch and consume the liquid. Being thin and lacking keratinization, the buccal membrane allows for rapid absorption, making this an appealing route for abusers. Chewing the patch is particularly dangerous due to the mechanical disruption of the patch, causing release of more than 72 hours worth of drug at one time. Liappas reported a case in which a 36-year-old woman was prescribed 25 mcg/hr fentanyl patches, three times daily.[10] Believing the drug was not appropriately penetrating her skin and providing her with adequate relief, the patient began to apply the patches to the oral cavity. The woman claimed she was able to achieve faster, more effective pain relief using this route. Over the course of several months, the patient increased the dose from 75 mcg/hr daily to 250 mcg/hr daily, totaling 10 patches, which she continued for 15 months. Due to her long-term abuse, the patient developed a high tolerance along with a strong dependence on fentanyl.

Street drug users also have been found misusing fentanyl patches, specifically, the newer matrix formulation.[7] Users are able to easily retrieve fentanyl by adding vinegar and water to the patch and allowing it to soak or by heating the patch. The resulting solution is placed in a container, from which users load a syringe and inject the drug intravenously. In addition to the increased risk of disease transmission, it is difficult to assess the potency of the drug because the quantity and time-released formulation make it impossible to know the amount of drug being injected. This presents a high risk of accidental overdose.

One of the less frequent, yet more dangerous, routes of administration is rectal insertion of the transdermal patch.[9] Similar to the buccal membrane, the rectal mucosa is non-keratinized, which, combined with the elevated

temperature, facilitates rapid absorption of fentanyl. In a case reported by Coon, a man was brought into the emergency room, unconscious after rectally inserting three 100 mcg/hr transdermal fentanyl patches. Upon admission, he was given 6 mg of naloxone, to which he did not respond, and was subsequently intubated. An hour after removal of the patches, the patient finally awoke. Acute onset of coma was attributed to elevation of serum fentanyl levels faster than usual, a direct result of the combination of the rapid absorption and number of high-dose patches inserted. The authors suggest that, in such cases, aggressive digital rectal examination, combined with anoscopy or sigmoidoscopy, should be utilized to ensure all internalized patches are recognized and removed.

A number of tactics are employed by potential fentanyl abusers in order to acquire the transdermal patches.[8,10] Methods include obtaining multiple prescriptions from more than one health care provider, illegal purchase from a drug dealer, theft from a patient who has a legitimate prescription, and removal from the trash or off of a person wearing a patch, including patients in a hospital or morgue.

Prevention and Treatment: The Role of Health Care Professionals

Several methods of monitoring patients who have been prescribed transdermal fentanyl have been proposed.[10] The major focus should be on the initial prevention of abuse, which could include requiring the original prescription and all follow-ups be conducted through specialized pain centers. Anticipation of drug-abuse potential and identification of populations at greater risk of abuse should be considered. Importance is also placed on recognition of abuse behavior and predisposition by thorough examination, including both family and social history of the prospective patient. Any signs of abuse or dependence should be identified and adequately addressed before a prescription is issued. Signs of opiate withdrawal include anxiety, enlarged pupils, excessive sweating, or an increase in blood pressure, pulse and temperature. To monitor for patient compliance and illicit drug use, urine and blood screenings should be encouraged. For those in which abuse of fentanyl has been identified, effective treatment may be most beneficially provided through facilities employing specifically trained psychologists or psychiatrists who can offer psychotherapeutic therapy to complement any required medical treatment. Considerations should be made to taper the patient off the drug in order to avoid withdrawal symptoms. Adding a weak opioid, such as codeine, to the therapy regimen can further facilitate this process.

Pharmacist Counseling Points

Due to its dangerous adverse effects, patients should be fully educated about the abuse potential, life-threatening dangers and proper disposal of fentanyl patches.[11] Pharmacists should consider a few points when counseling a patient:

- A medication guide must be provided with each dispensing.
- Patches are intended for transdermal use on intact skin only.
- Instruct patients not to use a patch if the package is broken or the patch is cut, damaged or altered.
- Avoid exposure of the application site to any external heating source because drug release may be increased, which could lead to overdose or death.
- Keep patches in a secure location away from pets, children and potential theft of the medication.
- Fentanyl's high potency and significant amount of drug remaining in used patches have resulted in manufacturer and FDA guidelines stating to fold the patch upon itself and immediately flush both used and leftover patches down the toilet.

Pharmacists need to be alerted to drug-seeking behaviors, including urgent refill requests or visits near the end of operating hours, "lost" prescriptions, altered prescriptions, and refusal or reluctance to disclose other medications or current physician(s). A common tactic among abusers is "doctor shopping" to obtain additional prescriptions and "pharmacy hopping" to fill multiple prescriptions for controlled substances.

Conclusion

With recent reports of transdermal fentanyl abuse on the rise, it is critical that pharmacists take an active role in preventing further perpetuation of abuse. This can be accomplished by awareness of the incidence and methods employed by abusers, including altering the patch or use via unintended routes of administration. Patients who have a legitimate need for this medication require proper education and monitoring to avoid abuse or accidental overdose or drug diversion. Health care professionals should be aware of signs and symptoms of abuse and proper treatment methods. Due to the highly potent nature and deadly adverse reactions associated with fentanyl, its misuse should not be taken lightly.

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